Management of Concurrent Pregnancy and Acute Lymphoblastic Malignancy in Teenaged Patients: Two Illustrative Cases and Review of the Literature

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The usual age range of acute lymphoblastic malignancies (acute lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma) includes teenagers and young adults (<22 years of age) and coincides with the age of fertility. Concurrence of acute lymphoblastic malignancy with pregnancy is therefore most likely to happen during the younger childbearing ages. However, the therapeutic challenges posed by the dual diagnosis of lymphoblastic malignancy and pregnancy have not specifically been studied in the context of age, and management guidelines for pregnant young patients are lacking. Inconsistency in defining the legal decision-making rights of pregnant teenaged patients adds a further level of complexity in this age group. Management of this challenging combination in the young patient therefore entails unique ethical considerations. Here we present two illustrative cases of teenage pregnancy complicated by acute lymphoblastic malignancy, review the available literature, and offer suggestions for the therapeutic management of such cases in adolescent and young adult patients. Importantly, practical management recommendations are provided in the context of clinical ethics principles that are universally applicable, including in developing countries, where the highest incidence of adolescent pregnancies has been documented.

Keywords: acute lymphoblastic leukemia, lymphoma, pregnancy, teenager, chemotherapy, teratogenicity

IN THE WESTERN WORLD, acute leukemia is diagnosed during 1 of every 75,000 to 100,000 adult pregnancies; two-thirds of these malignancies are acute myeloid leukemia and one-third are acute lymphoblastic leukemia (ALL).¹ To our knowledge, there is no available information about the incidence of lymphoblastic lymphoma during pregnancy, but the estimated general incidence of non-Hodgkin lymphoma is 0.8 cases per 100,000 pregnancies.²⁻⁴

ALL and advanced-stage lymphoblastic lymphoma have a very good prognosis in children and teenagers, and are currently treated on similar protocols.⁵ However, there are no available guidelines for the management of these cancers in pregnant young patients aged 21 years and younger. Here we provide a critical review of the available studies of these malignancies in the context of pregnancy. On the basis of these reports, our clinical experience, and clinical ethics principles, we suggest strategies for the management of acute

lymphoblastic malignancy in pregnant adolescents and in young women ≤ 21 years of age. We first present two clinical cases: one occurred in a low- to middle-income country and illustrates the influence of religious, sociocultural, and political pressures on medical decision-making; the second case occurred in a high-income country and demonstrates several difficult medical issues that must frequently be addressed when malignancy coincides with pregnancy.

Case Reports

Case 1

In July 2012, social and public media drew worldwide attention to the plight of a 16-year-old girl in a low-income setting who was diagnosed with ALL during her first trimester of pregnancy. She had presented at 9 weeks of gestation with a brief history of fever, pallor, and leg pain. On

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physical examination, she was febrile and pale and had an enlarged liver and spleen. Her hemoglobin concentration was 5 g/dL, white blood cell count was 91,000/mm³, and platelet count was 9000/mm³. A comprehensive metabolic panel and chest X-ray were within normal limits. Ultrasonography revealed a live fetus with growth appropriate for gestation. Bone marrow examination demonstrated precursor B-cell ALL. The cerebrospinal fluid showed no leukemic involvement.

The management of leukemia in this young patient was highly debatable. Multiagent chemotherapy during the first trimester carries a significant risk of fetal death, and abortion was punishable by imprisonment, loss of medical license, or both in the patient's country of residence. On the other hand, the fetus could not survive without a viable mother, and the mother's survival depended on rapid administration of antileukemic therapy. Therefore, the patient's physicians promptly sought permission from the nation's Ministry of Health to administer chemotherapy. Three weeks later, approval was granted and remission induction therapy was initiated at 12 weeks of gestation. The treatment protocol was composed of daunorubicin (45 mg/m² daily on days 1–3), vincristine (2 mg weekly × 4 doses), asparaginase (6000 IU/m²/day on days 5, 8, 11, 15, and 22), prednisolone (60 mg/m²/day × 21 days), and intrathecal methotrexate (12.5 mg on days 1 and 15). This was the standard induction protocol for adult ALL at the treating hospital, and was not modified for pregnancy. On day 15 of therapy, the bone marrow was hypoplastic and showed morphologic remission. Shortly thereafter, the patient was readmitted emergently with pulmonary hemorrhage and massive hemoptysis. Her coagulation profile revealed a low fibrinogen concentration (1.3 g/L) and platelet count (17,000/mm³). Supportive care (fresh frozen plasma, cryoprecipitate) was provided as possible, but its speed and extent were severely constrained by a lack of blood banking facilities, inadequate resources, and too few family donors. The patient experienced a spontaneous complete abortion and died on day 28 of therapy.

Case 2

A 17-year-old, 20-weeks-pregnant adolescent presented to a pediatric oncology unit with a 2-month history of a palpable right breast mass. She was otherwise asymptomatic, with an unremarkable medical history and systems review. A lumpectomy was performed, and tumor-tissue immunophenotypic markers were positive for CD19, CD38, cCD79a, CD10, and TdT, equivocal for CD34, and negative for CD20 and SIg. Her workup revealed a 6.6 cm mediastinal mass and bilateral breast involvement; the bone marrow contained 20% blast cells. Fluorescence *in situ* hybridization showed 28% of bone marrow cells to contain the *ETV6-RUNX1* [t(12;21)] fusion protein. The final diagnosis was advanced-stage⁶ precursor B-cell lymphoblastic lymphoma evolving to ALL.

The patient did not wish termination of her pregnancy but consented to a modified pediatric ALL treatment protocol.^{5,7} The modifications included withholding of asparaginase to reduce the risk of placental and venous thrombosis, withholding of systemic and intrathecal methotrexate until after delivery, and substitution of nebulized pentamidine for oral trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* pneumonia prophylaxis. Remission induction therapy started at

21 weeks of gestation and comprised prednisolone (40 mg/m²/day × 28 days), daunorubicin (30 mg/m² weekly × 4 weeks), and vincristine (2 mg weekly × 4 weeks), plus intrathecal cytarabine (50 mg) and hydrocortisone (50 mg) on days 7 and 28. At the end of induction therapy, the *ETV6-RUNX1* fusion signal was observed in 8% of bone marrow cells. One week later, at week 26 of gestation, she started a consolidation regimen of cyclophosphamide (1 g/m²/dose, 2 doses 28 days apart), cytarabine (75 mg/m²/dose, 4 doses/week × 4 weeks), and 6-mercaptopurine (60 mg/m² daily × 28 days). At the end of consolidation, she was in clinical and morphologic remission, although her bone marrow cells remained PCR-positive (1.6%) for the fusion protein.

In view of her persistent disease, a decision was made to perform an elective Cesarean delivery at week 32 of gestation. The patient was given betamethasone (12 mg intramuscular, in 2 doses 24 hours apart) to hasten fetal lung maturation. The mother's white blood cell count (7.1/mm³) and platelet count (267,000/mm³) were normal on the day of delivery. She delivered a boy with Apgar scores of 4 and 8 at 1 and 5 minutes after birth, respectively, and normal blood cell counts. The baby was electively intubated for administration of surfactant and was placed on continuous positive airway pressure ventilation. The infant experienced no significant complications and was discharged in good condition at 17 days of age. The placenta was histopathologically negative for leukemia/lymphoma involvement. The mother continued therapy with asparaginase, dexamethasone, methotrexate, and 6-mercaptopurine, as specified by the COG A5971 protocol.^{5,7} At the time of this report, she was receiving maintenance therapy and was in clinical, morphologic, and molecular remission.

Reviewed Articles

Although this report was not intended as a systematic review, we thoroughly searched the available literature, as summarized in Tables 1 and 2. Table 1 presents a summary of reviewed publications about concurrent cancer and pregnancy that contain analysis of data from original clinical studies evaluating outcomes for the mother, child, and pregnancy. Table 2 lists additional reviewed publications that also address cancer during pregnancy but did not present any analysis of original data. The tables do not list articles that were reviewed but not included in our references. Below is a description of our search methodology, which may not have identified all sources and databases.

Search strategy and selection criteria

Studies were selected for inclusion by searching the PubMed database for articles published from January 1, 1988 to January 31, 2014 using the search phrases "hematologic malignancy AND pregnancy," "leukemia/lymphoma AND pregnancy," and "leukemia chemotherapy AND pregnancy AND pregnancy outcome." Advanced filters included English language and available abstracts. Using similar search terms, articles were also identified by searching the Google Custom Search Engine FreeFullPDF (www.freefullpdf.com) and the MD Consult database (www.mdconsult.com).

Articles were selected for detailed review primarily on the basis of ALL or hematologic malignancy identified in the title or abstract as a pregnancy-associated diagnosis. Articles

TABLE 1. LITERATURE REVIEWED: PUBLICATIONS ABOUT CANCER IN PREGNANCY WITH ANALYSIS OF ORIGINAL DATA

<i>Authors (year of publication)</i>	<i>Journal article type^a</i>	<i>Study design and method</i>	<i>Type of cancer(s)</i>	<i>Date(s) of study</i>	<i>Number of evaluable cases</i>	<i>Maternal age (years)</i>	<i>Study aim(s)</i>
Amant et al. (2012) ⁴²	Original Research Article	Multicenter observational cohort study of children perinatally exposed to chemotherapy. Data collection was both retrospective and prospective.	Any	Began March 18, 2005	70 babies	Median = 32.9; range: 23.4–41.7	To assess the long-term general health, cardiac, and neurodevelopmental outcome in the study cohort.
Aviles, Neri, and Nambo (2012) ⁴⁹	Cancer Therapy	Prospective cohort study at a single institution. All cases diagnosed with hematologic malignancy in first trimester of pregnancy during the specified time period were studied prospectively. Median follow-up = 22.4 years (range: 3.8–32).	Hematologic malignancies	1975–2008	58 mothers 58 babies	23–39	To assess toxicity to mother and baby of chemotherapy during first trimester of pregnancy.
Gziri et al. (2012) ³⁵	Short Research Report	Prospective, case-control trial, single institution study. 10 fetuses exposed to anthracyclines compared to 10 control fetuses matched for sex and gestational age. The 10 mothers were compared to 10 non-pregnant women matched for age, type of cancer, and anthracycline treatment.	Breast cancer, hematologic malignancies	January 2010–September 2011	Mothers: 10 cases 10 controls Babies: 10 cases 10 controls	Not stated	To assess the risk of acute cardiac dysfunction in mother and fetus after exposure to anthracyclines during pregnancy.
Cardonick, Usmani, and Ghaffar (2010) ⁵¹	Original Article	Details of treatment and pregnancy outcome collected from cancer and pregnancy registry. Live born babies followed prospectively.	Any	August 1, 1995–September 1, 2008	157 babies	Mean in patients with acute leukemia = 30.4 ± 5.4	To report pregnancy outcome and long term follow-up findings in children exposed to chemotherapy <i>in utero</i> .
Peccatori et al. (2009) ⁶⁷	Clinical Trial	Multicenter clinical trial of weekly epirubicin in pregnant women at 16–30 weeks gestation, with locally advanced or metastatic breast cancer.	Breast cancer	January 2002–December 2007	20 mothers 20 babies	Median = 37; range: 23–42	Assess the safety and efficacy of weekly epirubicin in a clinical setting with no standardized treatment approach.

(continued)

TABLE 1. (CONTINUED)

<i>Authors (year of publication)</i>	<i>Journal article type^a</i>	<i>Study design and method</i>	<i>Type of cancer(s)</i>	<i>Date(s) of study</i>	<i>Number of evaluable cases</i>	<i>Maternal age (years)</i>	<i>Study aim(s)</i>
Van Calsteren et al. (2009) ⁵⁰	Original Report	International (Belgium, Netherlands, Czech Republic) collaborative cohort study. Cases identified and information gathered by direct communication with oncologists, hematologists, obstetricians, institutional data sets, and hospital registration systems.	Any	1988–2008	215 mothers 179 babies	Mean = 33.2 ± 4.8	Evaluate management options and the impact on neonatal and obstetric outcomes.
Pye et al. (2008) ³⁶	Clinical Trials and Observations	Retrospective review of case reports submitted by physicians to Novartis, the Hammersmith Hospital in London, and the MD Anderson Cancer Center in Houston.	Chronic myeloid leukemia	Not specified	180 mothers 145 babies	Not stated	Investigate the effect of gestational exposure to imatinib on the fetus and on the outcome of pregnancy.
Aviles, Neri, and Nambo (2006) ⁴⁷	Original Article	Prospective observational cohort study of children exposed to anthracyclines <i>in utero</i> and monitored for cardiac functional abnormalities to at least 20 years of age.	Acute leukemia, malignant lymphoma, Hodgkin disease	Not specified	81 babies	Not stated	Evaluate long-term cardiac toxicity after gestational exposure to anthracyclines.
Chelghoum et al. (2005) ³⁹	Original Article	Cases gathered retrospectively by mailed questionnaire from 13 treating centers in France.	Acute leukemia	December 1988–November 2003	37 mothers 23 babies	Median = 30; range: 19–45	Assess the effect of chemotherapy on pregnancy outcome, fetus, and cancer response.
Germann, Goffinet, and Goldwasser (2004) ³³	Original Article	Retrospective data collection from hospital-based patient registry and review of literature in Medline, Pascal, and Current Contents.	Any requiring anthracycline use	1976–2001	160 mothers 160 babies	Median = 27; range: 16–42	Retrospective analysis of effects of anthracyclines during pregnancy.
Aviles and Neri (2001) ⁴⁶	Original Contribution	Prospective observational cohort study. Cases were gathered from the medical records of the National Medical Center (oncology and specialist hospitals) in Mexico during the stated time period. Follow-up data on children were collected for a median of 18.7 years (range: 6–29).	Acute leukemia, malignant lymphoma, Hodgkin disease	1970–1995	84 babies	Not stated	Evaluate risk of acute and late side effects in children of mothers treated for hematologic malignancies during pregnancy.

(continued)

TABLE 1. (CONTINUED)

<i>Authors (year of publication)</i>	<i>Journal article type^a</i>	<i>Study design and method</i>	<i>Type of cancer(s)</i>	<i>Date(s) of study</i>	<i>Number of evaluable cases</i>	<i>Maternal age (years)</i>	<i>Study aim(s)</i>
Zemlickis et al. (1992) ³³	Original Investigation	Case control study: Pregnant patients receiving cancer chemotherapy during the indicated period were identified from hospital database and compared to age-matched pregnant women not exposed to chemotherapy.	Any	1958–1987	Study group = 21 mothers (21 babies) Control group = 21 mothers age-matched 1:1 with the study group	Mean = 27.4 ± 6.6	Analyze the effect of cancer chemotherapy on pregnancy.
Aviles et al. (1991) ⁴⁵	Original Article	Retrospective series of cases identified from the medical records of the Oncology Hospital, National Medical Center, Mexico. All living children were evaluated for chromosomal defects or growth and development abnormalities possibly attributable to chemotherapy exposure <i>in utero</i> . Disease outcome of mother also reported.	Hematologic malignancies	1970–1986	43 mothers 43 babies	19–28 in patients with acute leukemia	Evaluate the teratogenicity of chemotherapy given for hematologic malignancies.
Zuazu et al. (1991) ⁶⁸	Clinical Trial	Retrospective cross-sectional survey: Information gathered by mail questionnaire from 10 hospitals in Spain.	Hematologic malignancies	1974–1989	48 mothers 56 babies (21 exposed to chemotherapy <i>in utero</i> ; 35 not exposed)	20–37	Examine the relation between treatment of hematologic malignancy and pregnancy outcome.
Aviles et al. (1990) ⁴⁴	Original Research Article	Retrospective review of medical records to evaluate management and outcome of non-Hodgkin lymphoma during pregnancy.	Non-Hodgkin lymphoma	1975–1986	16 mothers 16 babies	18–34	Analysis of single center experience in management of non-Hodgkin lymphoma during pregnancy.
Aviles and Niz (1988) ²⁴	Article	Prospective cohort study: All children at Mexico's National Medical Center who had <i>in utero</i> exposure to chemotherapy, 1963–1981 were followed prospectively for acute and long-term effects.	Acute leukemia	1963–1981	18 mothers 20 babies	Not stated	Effect of gestational exposure to chemotherapy on physical health, growth, and development of live-born babies.

^aArticle type as designated by publishing journal.

TABLE 2. LITERATURE REVIEWED: PUBLICATIONS ABOUT CANCER IN PREGNANCY WITHOUT ANALYSIS OF ORIGINAL DATA

<i>Authors (year of publication)</i>	<i>Publication type</i>	<i>Purpose of publication</i>
Horowitz et al. (2013) ¹⁴	Journal article	Systematic review of articles published 1967–2011 to determine characteristics, management, and outcome of non-Hodgkin lymphoma during pregnancy
Vandenbriele et al. (2013) ¹³	Electronic book section	Review of available data about diagnosis and chemotherapeutic treatment of hematologic malignancies during pregnancy and general approach to management of cancer in pregnancy.
Brenner, Avivi, and Lishner (2012) ¹⁰	Journal article	Updated guidance on management of pregnancy-associated hematologic malignancies with chemotherapy and biological agents.
El-Hemaidi and Robinson (2012) ²⁸	Electronic book chapter	Review of published literature to provide guidance on management of hematologic malignancies during pregnancy.
Gziri et al. (2012) ³⁴	Journal article	Review of literature on co-occurrence of cancer and pregnancy specifically to analyze the maternal and fetal cardiotoxic effects of chemotherapy.
Han et al. (2012) ¹⁷	Journal article	Evaluate treating physicians' attitudes and knowledge about treatment options for pregnant patients with cancer using an electronically mailed questionnaire.
Perez et al. (2012) ⁴	Journal article	Case report of non-Hodgkin lymphoma treated with aggressive combination chemotherapy (R-CHOP) in 2nd trimester with good outcome of pregnancy, baby, and primary disease 1-year post-delivery.
Abadi, Koren, and Lishner (2011) ⁹	Journal article	Review of therapeutic options for hematologic malignancies during pregnancy and discussion of optimization of therapy for mother with minimal risk to baby.
Voulgaris, Pentheroudakis, and Pavlidis (2011) ¹	Journal article	Review of literature to gather information about diagnosis, management, and outcome of cancer during pregnancy.
Azim, Pavlides, and Peccatori (2010) ²⁶	Journal article	Systematic review of data published 1980–March 2009 to discuss the safety of different chemotherapy regimens for hematologic malignancies during pregnancy and to propose alternatives when standard treatment poses significant risk to the fetus.
Aviles A (2009) ⁴³	Journal article	Review of the literature to evaluate maternal and fetal risk after cytotoxic chemotherapy during pregnancy.
Rizack et al. (2009) ¹¹	Journal article	Review of data published January 1, 1980–December 31, 2008 to formulate suggestions for management of all types of hematologic malignancy during pregnancy.
Matsouka et al. (2008) ⁴¹	Journal article	Case report of a teenaged patient treated for acute lymphoblastic leukemia during 2nd trimester with good outcome for the baby and maternal disease.
Pereg, Koren, and Lishner (2008) ⁸	Journal article	Review of available data on different aspects of diagnosis and treatment of cancer during pregnancy and the effect of pregnancy on cancer prognosis.
Shapira, Pereg, and Lishner (2008) ¹²	Journal article	Critical review of available literature to identify clinical, ethical, and other challenges and suggest options for management of all types of leukemia during pregnancy.
Pentheroudakis and Pavlidis (2006) ³	Journal article	Critical review of available evidence about the incidence, epidemiology, and genetics of cancer in pregnancy and its clinical features and diagnostic and management issues.
Hurley, Kinnell, and Irani (2005) ²	Journal article	Discussion of common hematologic malignancies and case vignettes to illustrate importance of early diagnosis for a positive maternal and fetal outcome. Includes discussion of treatment options during pregnancy.
Leslie, Koil, and Rayburn (2005) ⁶⁰	Journal article	Review of the literature about the effects of specific chemotherapeutic agents on mother and fetus during pregnancy.
Cardonick and Iacobucci (2004) ²⁰	Journal article	Review of use of chemotherapy during pregnancy and reported neonatal outcomes.
Oduncu et al. (2003) ⁵⁴	Journal article	Review of the literature on co-occurrence of cancer and pregnancy to discuss the complex issue of optimal maternal treatment with minimal fetal harm.
Pavlides (2002) ¹⁹	Journal article	Review of cancers commonly seen during pregnancy, the safety of diagnostic and therapeutic approaches during pregnancy, the reported metastatic patterns in placenta and fetus, and recommendations for elective abortion.
Weiz, Schiff, and Lishner (2001) ¹⁸	Journal article	Review of available data on the impact of coexistent cancer and pregnancy on the course of the disease, its treatment, and the outcome for mother and fetus.
Doll, Ringenberg, and Yarbrow (1988) ²³	Journal article	Review of available data to help with difficult decisions regarding pregnancy termination, use of radiation and chemotherapy, and the risk of fetal exposure to teratogenic therapy.

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine.

were narrowed to those that specified the chemotherapeutic agents used, gestational age at the time of therapy, and pregnancy outcome and/or long-term follow-up results. We occasionally selected articles that did not address lymphoblastic malignancies but did discuss the chemotherapeutic agents used to treat these malignancies.

Discussion

Clinical evaluation, diagnosis, and staging of hematologic malignancy in pregnant patients

Pregnancy is a unique physiologic state involving the complex interplay of anatomic, functional, and endocrine changes, in which clinical and laboratory findings may mimic hematologic malignancy. It can be extremely difficult during early stages to differentiate pregnancy-related physiologic changes from the subtle, early signs of an evolving acute malignancy, and this mimicry may delay a cancer diagnosis.^{1,8–13} Interestingly, a recent systematic review of non-Hodgkin lymphoma (NHL) in pregnancy observed that aggressive forms of NHL exhibit unique clinical and biological features during pregnancy, including frequent involvement of the reproductive organs (breast, ovary, uterus, and placenta).¹⁴ This finding was reported in 100% of cases of endemic Burkitt lymphoma and 70% of cases of non-endemic Burkitt lymphoma; in other forms of aggressive NHL the incidence was 23–67%, still much higher than that in non-pregnant women of reproductive age.¹⁴ These atypical features can be mistaken for the expected benign findings associated with pregnancy, partially explaining the delayed recognition of malignant disorders during this time.^{8,14} The patient in our second case had a history of breast mass pre-dating the diagnosis of NHL by several weeks.

Mild to moderate thrombocytopenia, leukocytosis, and anemia are frequent findings in normal pregnancy. Pregnant teenage girls are especially susceptible to severe anemia because of the high iron requirements of their own continued, rapid growth. In developing countries, comorbidities such as dietary iron deficiency and hookworm infestation may exacerbate this complication.¹⁵

Pregnancy also induces a state of hypercoagulability, a physiological mechanism aimed at averting excessive bleeding during delivery. Pregnancy alone increases the risk of thromboembolism by a factor of 4 to 5, and this risk is doubled with Cesarean delivery.¹⁶ Coexisting hematologic malignancy markedly exacerbates the risk of leukocytosis, deep vein thrombosis, and disseminated coagulopathy; it also increases the risk of placental thrombosis or insufficiency, which can result in low birth weight. Prophylactic administration of low-molecular-weight heparin is considered to be safe for pregnant patients at high risk.¹⁰

The workup of lymphoma entails disease staging through detailed imaging studies. The cumulative radiation exposure of a fetus during routine diagnostic procedures, excluding abdominal and pelvic computed tomography (CT) scans, is estimated to be < 10 cGy. At these doses, no increase in fetal death, growth retardation, or congenital malformation has been observed.^{8,13,17,18} However, abdominal and pelvic CT scans and [18F]fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography scans entail high radiation exposure and are not recommended during pregnancy.⁸ Iodinated contrast agents are deemed safe during pregnancy, allowing the use of gadolinium-enhanced magnetic

resonance imaging.¹³ It is important to assess fetal risk in the context of gestation stage, as the expected severity of damage is greatest during organogenesis, weeks 2–8.¹⁹

Teratogenicity of chemotherapeutic agents

Most cytotoxic drugs have been teratogenic in animal studies, although the doses used in humans are below the minimally teratogenic doses in animals.^{9,20} The placenta is an inefficient barrier to cytotoxic drugs, allowing the passage of molecules < 600 kDa (including almost all cytotoxic agents).^{10,12} The comparative teratogenicity of individual chemotherapeutic agents depends on their molecular weight, ionization state, lipid solubility, and binding affinity to plasma proteins; therefore, low-molecular-weight, non-ionized, highly lipid-soluble, and loosely protein-bound drugs are able to cause the greatest fetal harm.^{1,10,12,21} However, the most crucial determinant of teratogenicity is the gestational timing of exposure. Exposure during the first two weeks produces an “all or nothing” effect, meaning either loss of pregnancy or no lasting damage.²² The most vulnerable period for congenital malformations is the first trimester, especially weeks 2–8. Cytotoxic drugs during this period can cause malformations of the heart, neural tube, limbs, palate, and ears.²⁰

On the whole, the risk of congenital malformation after chemotherapy for cancer appears to be lower in humans than estimates Zuazu et al. (Table 1) demonstrated no difference in fetal complications after *in vivo* cytotoxic exposure, compared to normal.⁶⁸ The overall risk of teratogenicity during the first trimester is considered to be 10–20%;^{1,8} the risk is 10% after the use of a single chemotherapeutic agent and 15–25% after combination chemotherapy.^{8,9,11,12,23} The greatest risks are from alkylating agents and antimetabolites; vincristine poses the lowest risk.¹¹ However, in a prospective study by Aviles and Niz of 20 children exposed *in utero* to intensive ALL chemotherapy between 1963 and 1981 (11 of which were exposed during the first trimester), none showed any congenital malformation, chromosomal abnormality, or late-onset cardiac or neurologic toxicity during follow-up periods ranging from 4 to 22 years.²⁴ The most commonly reported outcomes of cytotoxic insult during the first trimester are intrauterine fetal demise or spontaneous abortion,^{8,12,25} as in our first case illustration. After the first trimester, the risk of congenital malformation falls to approximately 3%, similar to the risk in the general population.^{11,25} During this period the fetus acquires functional maturity; therefore, cytotoxicity during this time has implications for functional—rather than anatomic—defects. The organs at functional risk during this phase are the central nervous system, hematopoietic system, eyes, and ears.²⁰ However, the most commonly documented consequences during the late second or third trimester are intrauterine growth retardation, premature birth, and low birth weight.²⁶ Stillbirth and spontaneous abortion have also been reported, but are very rare after the first trimester.

Fetal effects of individual drugs for lymphoblastic malignancies

Cytotoxic agents used to treat lymphoblastic malignancies (Table 3) cause alopecia and reversible pancytopenia in the fetus. The maternal blood count nadir occurs approximately two weeks after chemotherapy; therefore, elective delivery

TABLE 3. DRUGS FOR ACUTE LYMPHOBLASTIC MALIGNANCY DURING PREGNANCY: FETAL/NEONATAL EFFECTS AND RECOMMENDATIONS

<i>Cytotoxic agent</i>	<i>Effect on fetus/newborn</i>	<i>Recommendation</i>
Any	Reversible pancytopenia, alopecia.	Avoid after week 35 or within 2–3 weeks of planned delivery.
Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) ^{1,11,12,20,26,28,67}	<i>1st trimester:</i> Limb abnormalities. <i>2nd/3rd trimester:</i> Preeclampsia, IUGR, IUFD, miscarriage (especially with idarubicin). Cardiomyopathy in newborn documented with idarubicin.	<i>Doxorubicin:</i> Preferred choice during pregnancy. <i>Daunorubicin/epirubicin:</i> Intermediate choice. <i>Idarubicin:</i> Contraindicated.
Asparaginase ^{2,27,29,32}	Animal studies show fetal skeletal abnormalities with <i>E. coli</i> asparaginase. ³² Human studies of single-agent asparaginase not available. Low birth weight documented after asparaginase in multiagent chemotherapy.	Use with caution ONLY when clearly indicated, after careful consideration of risk versus benefit.
Corticosteroids (dexamethasone, prednisolone) ^{12,22}	<i>1st trimester:</i> Animal studies show 3.4-fold greater risk of oral cleft. Increased risk of PROM, gestational diabetes, hypertension.	Monitor newborn for adrenal insufficiency and infection.
Cyclophosphamide ^{2,4,13,19,20,27}	Non-specific teratogenicity in 6 of 11 (55%) single-agent exposures reported. This contrasts with several reports of use in combination protocols without adverse outcomes.	<i>1st trimester:</i> Pregnancy termination. <i>2nd/3rd trimester:</i> Treat as non-pregnant.
Cytarabine ^{11,12,20,26}	<i>1st trimester:</i> Limb and ear malformations, IUFD, IUGR documented after systemic therapy.	<i>1st trimester:</i> Pregnancy termination. <i>2nd/3rd trimester:</i> Treat as non-pregnant.
Methotrexate ^{12,13,16,28}	<i>1st trimester:</i> Congenital anomalies, increased risk of miscarriage. <i>2nd/3rd trimester:</i> At doses > 10 mg/week: cranial dysostosis, hypertelorism, wide nasal bridge, delayed ossification, micrognathia, and ear abnormalities (aminopterin syndrome).	< 20 weeks GA: Pregnancy termination. 20–28 weeks GA: Consider modified therapy without methotrexate. <i>3rd trimester:</i> Treat as non-pregnant with informed consent.
6-thioguanine and 6-mercaptopurine ²⁷	Risk of single-agent exposure not known. 1st trimester exposure in combination with other chemotherapy has shown ~30% overall risk of teratogenic effects.	<i>1st trimester:</i> Use with caution. <i>2nd/3rd trimester:</i> Treat as non-pregnant.
Tyrosine kinase inhibitors (dasatinib, imatinib, nilotinib) ^{1,27,36–38}	Congenital anomalies, especially of kidneys, gut, brain, heart, skeleton. Risk greatest during first trimester.	<i>1st trimester:</i> Contraindicated. <i>2nd/3rd trimester:</i> Avoid if possible. Exercise extreme caution; use where benefit to mother clearly outweighs risk to fetus.
Vincristine ^{1,11,16,45}	No congenital anomalies or neurotoxicity documented.	No evidence to restrict use during pregnancy.

GA, gestational age; IUFD, intrauterine fetal demise; IUGR, intrauterine growth retardation; PROM, premature rupture of membranes.

should be delayed for at least three weeks after the cessation of chemotherapy.¹² This delay also allows time for fetal elimination of drugs via the placenta, averting excessive renal burden in newborns, especially preterms. Chemotherapy is not recommended after week 35, as spontaneous labor and premature delivery are more likely at this time¹³ and may occur during maternal/fetal peripheral blood nadir.

Methotrexate acts as an abortifacient and produces a combination of congenital anomalies termed “aminopterin syndrome” (Table 3).^{27,28}

6-Thioguanine and *6-mercaptopurine* are associated with a 32% and 29% overall rate of congenital malformation, respectively, when used in combination chemotherapy in the first trimester; however, the risk incurred by single-agent exposure is not established.²⁷

Corticosteroids were not highly teratogenic in a prospective study by Koren and Lishner of 184 women exposed during pregnancy.²²

L-asparaginase derived from *Escherichia coli* or *Erwinia chrysanthemi* significantly reduces the level of coagulation

TABLE 4. SUMMARY OF REPORTED SHORT- AND LONG-TERM OUTCOMES OF CHEMOTHERAPY EXPOSURE DURING GESTATION

Authors (year of publication)	Total cases studied		Total acute leukemia cases (n with ALL)	Maternal outcome	Started treatment during pregnancy (trimester)	Abortion (n)		IUD (n)	Delivery		IUGR/LBW (n)	Congenital anomalies (n)		Neonatal death (n)	Long-term adverse effects	(Comments)/Study conclusion(s)
	W	B				S	E		Premature (weeks)	Term >37 weeks (n)		N	M			
Amant et al. (2012) ⁴²	68	70	7 (5)	NS	70 (2–3)	0	0	0	7 (<32) 9 (32–33.9) 31 (34–36.9)	9	14	5	2	0	Yes (neuro-developmental delay in twin babies, <i>n</i> = 2)	– (Of 70 babies, 27 were studied retrospectively and 43 were studied prospectively). – General health, growth, CNS, cardiac, and auditory development did not differ from population norms. – (The ONLY reported prospective study of long-term outcome of mother and child. Median follow-up = 22.4 years) – Curative chemotherapy for mothers is possible during 1st TM without permanent effects on the fetus.
Aviles, Neri, and Nambo (2012) ⁴⁹	58	58	46 (6)	43 ADF 6 AWD	58 (1)	2	0	2	4 (<32)	40	10	0	0	0	No	– In fetuses exposed to chemotherapy after the 1st TM, congenital anomalies, preterm delivery, and growth retardation were no greater than in the general population. – Overall good pregnancy outcome.
Cardonick, Usmani, and Ghaffar (2010) ⁵¹	152	157	3 (NS)	NS	150 (2–3) 2 (1)	0	13	1	9 (NS)	135	12	6	0	0	No	– Optimal timing for elective delivery = 35–37 weeks. – Chemotherapy during 2nd and 3rd TM does not increase risk of congenital malformation.
Van Calsteren et al. ⁵⁰ (2010)	215	179	11 (4)	NS	122 (2–3)	5	30	1	15 (<32) 82 (32–37)	82	26	7	0	0	NS	– Weekly epirubicin is a feasible and safe for treating advanced breast cancer during pregnancy. – (Long-term follow-up of cardiac function in children reportedly normal at birth after <i>in utero</i> chemotherapy exposure). – No clinical or echocardiographic evidence of late cardiac toxicity after exposure to anthracyclines.
Peccatori et al. (2009) ⁶⁷	20	20	0	14 ADF 3 AWD 3 Dead	20 (2–3)	0	0	0	1 (28)	19	NS	1	0	0	0	
Aviles, Neri, and Nambo (2006) ⁴⁷	81	81	29 (NS)	NS	81 (NS)	NS	NS	NS	NS	NS	NS	NS	NS	NS	No	

(continued)

TABLE 4. (CONTINUED)

Authors (year of publication)	Total cases studied		Total acute leukemia cases (n with ALL)	Maternal outcome	Started treatment during pregnancy (trimester)	Abortion (n)		IUD (n)	Delivery		IUGR/LBW (n)	Congenital anomalies (n)		Neonatal death (n)	Long-term adverse effects	(Comments)/Study conclusion(s)
	W	B				S	E		Premature (weeks)	Term >37 weeks (n)		N	M			
Chelghoum et al. ³⁹ (2005)	37	37	37 (6)	12 Dead 25 A-NOS	9 (1) 10 (2) 11 (3)	1 1 0	8 5 0	0 0 0	0 1 2	22 3 9	NS	NS	NS	NS	NS	– (7 of 18 patients in 3rd TM had delay of chemotherapy until after delivery; they are not included in this table). – Pregnancy termination may not be necessary for chemotherapy during 2nd and 3rd TM with fetal surveillance and monitoring.
Germann, Goffinet, and Goldwasser (2004) ³³	160	160	80 (NS)	6 Dead 154 A-NOS	31 (1) 103 (2) 26 (3)	2 1 1	0 0 0	1 9 5	0 9 1	20 84 19	NS	0 0 0	3 2 0	0 0 0	NS	– Anthracyclines can be toxic to the fetus, but risk seems low especially in 1st TM and when dose of doxorubicin is less than 70mg/m ² . – No significant abnormality in children exposed to chemotherapy <i>in utero</i> , at birth, or through median follow-up of 18.7 years. – Full doses of chemotherapy can be given during pregnancy, even during 1st TM, when cure is a reasonable possibility.
Aviles and Neri (2001) ⁴⁶	84	84	29 (10)	62 ADF 22 Dead	38 (1) 46 (2–3)	NS	NS	NS	NS	84	NS	NS	NS	0	No	– Study confirmed risk of spontaneous abortion and major anomalies with treatment during 1st TM but not in later gestation. – Women should be monitored closely during pregnancy because of high risk of stillbirth and IUGR.
Zemlickis et al. (1992) ⁵³	21	21	4 (0)	NS	13 (1) 4 (2) 4 (3)	4 0 0	4 1 0	0 1 0	0	5 2 4	4 2 4	0 0 0	2 0 0	0	No	– Follow-up 3–19 years after birth showed chemotherapy can be administered at full doses during pregnancy, even 1st TM, without physical, neurological, or cytogenetic abnormalities.
Aviles et al. (1991) ⁴⁵	43	43	7 (4)	17 Dead 25 ADF 1 LFU	19 (1) 24 (2–3)	0 0	0 0	0 0	1 2	18 22	0	0 0	0 0	0	No	– Women should be monitored closely during pregnancy because of high risk of stillbirth and IUGR.

(continued)

TABLE 4. (CONTINUED)

Authors (year of publication)	Total cases studied		Total acute leukemia cases (n with ALL)	Maternal outcome	Started treatment during pregnancy (trimester)	Abortion (n)		IUD (n)	Delivery		IUGR/LBW (n)	Congenital anomalies (n)		Neonatal death (n)	Long-term adverse effects	(Comments)/Study conclusion(s)
	W	B				S	E		Prenature (weeks)	Term >37 weeks (n)		N	M			
Zuazu et al. (1991) ⁶⁸	48	56	15 (2)	2 Dead 46 A-NOS	5 (1) 16 (2-3)	2 1	2 2	0 2	0	1 11	0 0	0 0	0 0	0	No	- (35 of the 56 babies were NOT exposed to chemotherapy <i>in utero</i> ; their results not presented in this table). - The data suggested that chemotherapy for hematologic malignancy, if deemed necessary, should not be postponed because of pregnancy. - Pregnancy does not contraindicate treatment of NHL. - Cytotoxic drugs do not necessarily cause congenital malformations, and long-term remission can be achieved. - Chemotherapy was not associated with excessive risk to fetus even during 1st TM. - (Maternal deaths were due to relapse 2-7 years after childbirth - Neonatal deaths 21 days and 90 days after birth were due to infection.
Aviles et al. (1990) ⁴⁴	16	16	0 (2 LL)	8 ADF 7 Dead 1 LFU	8 (1) 8 (2-3)	0	0	0	0	16	6	0	0	0	No	
Aviles and Niz (1988) ²⁴	18	20	18 (12)	5 ADF 13 Dead	11 (1) 7 (2-3)	0	0	1	0	19	3	0	0	2	No	

A-NOS, alive but not otherwise specified; ADF, alive and disease-free; ALL, acute lymphoblastic leukemia; AWD, alive with disease; B, babies; CNS, central nervous system; E, elective; IUD, intrauterine death; IUGR, intrauterine growth retardation; LBW, low birth weight; LFU, lost to follow-up; LL, lymphoblastic lymphoma; M, incidence more than normal population; N, incidence same as in normal population; NHL, non-Hodgkin lymphoma; NS, not stated; S, spontaneous; TM, trimester; W, women.

inhibitors (e.g., anti-thrombin III) and carries a substantial risk of thrombosis in adults and children with ALL.^{2,27,29,30} The risk of L-asparaginase-induced coagulopathy in childhood ALL increases with age and is highest in adolescents;³¹ this risk may be expected to be exacerbated during pregnancy, which itself is a hypercoagulable state, but only limited data from animal studies are available. L-asparaginase during the first trimester was shown in preclinical studies to produce congenital malformations in 17% of viable fetuses and resorption of 57% of implanted embryos.³²

Vincristine is considered the least teratogenic of the anti-mitotic agents. The documented malformation rate is no more than 10% after first-trimester exposure,²⁷ as vinca alkaloids—with their high affinity for protein binding—cross the placenta poorly.

Anthracyclines. The transplacental passage of anthracyclines in humans is not well characterized and there is no conclusive evidence that the drug reaches the fetus.³³ A recent review of the cardiotoxicity of chemotherapeutic agents proposed a policy of fetal cardiac monitoring and surveillance during and after *in utero* exposure to anthracyclines.³⁴ However, prospective long-term follow-up by (Table 4), and a more recent prospective case control study by Gziri et al. (Table 1) failed to show any long-term clinical or echocardiographic evidence of cardiac toxicity after fetal exposure to anthracyclines.^{35,47} Cardonick and Iacobucci, however, demonstrated non-cardiac congenital abnormalities resulting from fetal anthracycline exposure²⁰ (Table 3). Idarubicin is contraindicated during pregnancy due to its high lipid solubility,³ while doxorubicin has the best safety. Peccatori et al. demonstrated low fetal toxicity with epirubicin in a clinical trial.⁶⁷

Cyclophosphamide has been studied in 209 cases, with a 26% rate of adverse pregnancy outcomes overall and a 22% rate of fetal malformation after first-trimester exposure.²⁷ However, most reported cases have involved combination chemotherapy, and several studies have documented safe maternal and fetal outcomes after standard cyclophosphamide-containing regimens for aggressive lymphomas during pregnancy.^{2,4,13,19,20}

Cytarabine exposure during the first trimester has been found to pose an 11% risk of congenital anomalies,²⁷ while second- and third-trimester exposure is associated with increased risk of prematurity, low birth weight, and possibly intrauterine fetal demise.^{12,26}

Imatinib, the prototype tyrosine kinase inhibitor, has been teratogenic in animal studies. Selig et al. reported the largest review of human teratogenic effects of chemotherapeutic agents; they included 24 cases of imatinib exposure during pregnancy, which had a 21% cumulative incidence of adverse pregnancy outcome.²⁷ A retrospective review of adverse imatinib-associated events reported by physicians to the manufacturer (Novartis) documented 12 serious congenital anomalies among 125 evaluable pregnancies; 9 of the 12 involved first-trimester exposure.³⁶ There is limited experience in the use of second-generation tyrosine kinase inhibitors such as dasatinib and nilotinib during pregnancy, but these too have been documented to produce teratogenic effects.^{37,38}

Pregnancy outcome after chemotherapy for ALL

Because of the rarity of intensive multiagent ALL chemotherapy during pregnancy, there are few well-controlled

studies of its effects. However, despite the fetal toxicities of individual chemotherapeutic agents (Table 3), several retrospective^{1,9–12,39–42} and prospective^{24,43–49} studies of the long-term effects of *in utero* chemotherapy exposure suggest that standard combination chemotherapy for ALL—even during the first trimester—is not associated with any long-term serious consequences in the child (Table 4).^{24,39,42,44–47,49,50} The most commonly reported adverse outcomes of pregnancy after first-trimester exposure are spontaneous abortion and intrauterine fetal death; second- or third-trimester exposure is more commonly associated with intrauterine growth retardation and low birth weight.^{20,51–53}

Ethical considerations and treatment recommendations

Acute lymphoblastic malignancy requires urgent treatment, as life expectancy without therapy is less than 8 weeks.⁵⁴ A dual diagnosis of cancer necessitates complex and often emotionally charged decision-making that must balance the risk of cancer to the mother against the risk of cancer treatment to the developing fetus, all while under the pressure of time. Such decisions are even more complex with adolescent patients, who remain minors but also have an increasing voice in their medical decisions. Further, pediatric oncologists often have limited experience in treating pregnant patients and may experience moral distress about the most ethically appropriate way to proceed. The physician must judge the ability of the adolescent to comprehend the implications of medical decisions for herself and her baby. While many countries and many states in the United States allow pregnant teenagers to solely provide consent, we encourage clinicians to advocate for the participation of an adult trusted by the patient.⁵⁵

Four ethical principles are important while considering cancer treatment for pregnant teenagers. First is the physician's foremost professional (*fiduciary*) responsibility to protect and promote the interests of the teenaged patient. Second, the principle of *patient autonomy* demands respect for the patient's values and beliefs, regardless of the physician's personal or professional opinion. Third, the principle of *beneficence* demands actions that specifically benefit the patient or that provide a greater balance of benefit than harm.^{56,57} And fourth and final, the principle of *non-maleficence* requires interventions that may result in harm to be minimized.

When treatment of maternal malignancy offers a chance of cure to the mother without causing risk of iatrogenic morbidity or mortality to the fetus, the beneficence-based options are said to be congruent and physicians are ethically justified in influencing decision-making through professional recommendation. However, beneficence-based responsibilities of the physician become incongruent when the benefit of cancer treatment for the mother is contradicted by the risk of therapy-related fetal harm. In such cases, the processes of counseling and informed consent should include the issue of fetal viability.

The purpose of informed consent is to help a patient exercise her right to autonomy in a discerning manner.⁵⁸ The informed consent process should highlight the necessity of cancer therapy for the mother while acknowledging the potential iatrogenic risks to the fetus, clarifying that a previable

fetus cannot survive unless its mother also survives. In view of the uncertain effects of cancer therapy on the fetus, the mother should be provided with three treatment options: (1) decline pregnancy termination, start therapy with close fetal monitoring and reconsider termination if significant fetal side effects are detected during the previsible period, (2) electively terminate pregnancy before the start of therapy, or (3) delay treatment until fetal lung maturity to allow elective premature delivery before starting chemotherapy.⁵⁷ The last option does not apply to aggressive malignancies such as ALL and advanced-stage lymphoblastic lymphoma for which even a brief delay may pose a high risk of mortality to both mother and fetus.

Physicians with strong personal beliefs about pregnancy termination may wish to follow institutional policy to transfer the patient's care to another physician. Counseling about pregnancy termination before the start of cancer therapy should be non-coercive, non-directive and focused on the risks and benefits of the procedure in the context of the mother's disease and its outcome. When elective abortion is not acceptable to the mother, it is important to clarify that fetal loss is a potential complication of cancer treatment but is not the intended outcome. It is important to clearly differentiate unintended but likely fetal demise from direct, intentional abortion. In such cases, the physician should select a remission induction regimen that poses minimal risk to the fetus (demonstrating the ethical principle of nonmaleficence) while maintaining efficacy for the benefit of the mother (beneficence).

In treating curable malignancies such as ALL and lymphoblastic lymphoma, it is important to maintain curative intent and to start treatment immediately after obtaining informed consent. Less experienced pediatric oncologists often refer pregnant teenagers to adult oncologists, although treatment with pediatric protocols provides a consistent prognostic advantage to adolescents and young adults.⁵⁹ In the absence of guidelines for the management of acute lymphoblastic malignancy in adolescents and young adults, our review of the literature suggests induction chemotherapy with oral prednisolone or dexamethasone, vincristine, and daunorubicin in the usual protocol-directed doses.^{8,11,12,20,28} Intrathecal methotrexate must not be used before 28 weeks of gestation; however, if the mother opts against strongly recommended pregnancy termination, methotrexate can be replaced with intrathecal hydrocortisone and cytarabine (pregnancy risk category D, the benefit justifies risk to fetus)^{11,52,60} after the patient is fully informed about potential limb abnormalities.^{2,11,12,20,60} L-asparaginase should be avoided throughout pregnancy (Table 3) unless the expected benefit outweighs the significant risk of thromboembolism.² Supportive care for nausea and vomiting can be safely provided during early pregnancy with ondansetron, metoclopramide, or antihistamines.^{12,61,62}

For consolidation chemotherapy, we recommend Berlin-Frankfurt-Münster-based combination chemotherapy⁶³ utilizing cyclophosphamide, cytarabine, and 6-mercaptopurine but avoiding intrathecal methotrexate before week 28 of pregnancy, and withholding asparaginase throughout pregnancy.

Chemotherapy should be stopped altogether after week 35 of pregnancy to allow fetal bone marrow recovery and safe elective delivery after 37 weeks of gestation.^{12,13}

Procedures needed to assess response to therapy (bone marrow aspiration and cerebrospinal fluid examination) pose no additional risk and should proceed according to protocol recommendations.

As a rule, when cancer is diagnosed late in pregnancy, therapy should be delayed until after birth, provided there is no undue risk to the patient. In the case of aggressive malignancy for which treatment cannot be safely delayed (e.g., ALL or advanced-stage lymphoblastic lymphoma), fetal lung maturity should be assessed. If the lungs are mature, or if maturity can be sufficiently accelerated by steroid administration, elective premature delivery with all appropriate safety precautions should be planned. We suggest that an interdisciplinary team involving neonatology, obstetrics, and oncology should meet to develop a comprehensive plan of care for a patient whose fetus is approaching viability or would be delivered prematurely. Such a team can not only plan for optimal treatment but also help the patient understand the risks of a preterm or extremely premature delivery, as well as what to expect afterward. When premature delivery is not safe or is declined by the patient, standard induction chemotherapy (without asparaginase) should be started, with informed consent. Chemotherapy should be withheld after week 35 to allow the recovery of blood cell counts and to plan the timing for elective delivery.¹²

Shared decision-making is the ideal model for resolving difficult questions. The intersection of pregnancy and malignancy entails complex decisions, as the interests of the patient and the developing fetus are often at odds. If the need for treatment is urgent, it should not be delayed by concern about the fetus, whose survival depends absolutely on survival of the mother. Some families readily elect to proceed with therapy or to terminate the pregnancy and focus on cancer treatment, while others need time to compare the risks and benefits of the treatment options within the context of their personal and religious values, the cancer prognosis, and the stage of pregnancy. While we encourage a process in which decision-making is shared by the family and clinicians, it is important that clinicians make only evidence-based recommendations grounded in research reports or clinical experience and avoid making recommendations based on their personal beliefs. Forced termination of pregnancy or any therapy decision contrary to the patient's wishes is highly discouraged, and may cause long-term adverse psychosocial outcomes for the patient.⁶⁴ The young patient's developing autonomy should be respected and her voice be heard. Consultation with an experienced service focused on quality of life or ethics can be invaluable in helping teenagers, families, and clinicians arrive at a mutually satisfactory treatment plan.

International considerations

The global incidence of adolescent pregnancy is not known with certainty; however, the World Health Organization estimated that during 2000–2005, females 15–19 years old had 25.9 million pregnancies and 16.3 million live births.⁶⁵ Almost 95% of adolescent pregnancies occur in developing countries, where the adolescent fertility rate is documented to be more than twice that in developed countries.⁶⁵ In 2007, UNICEF reported that more than 25% of adolescent childbirths occur in the world's least developed countries.⁶⁶ The incidence of adolescent ALL therefore

parallels the greater frequency of adolescent pregnancy in resource-poor countries, and is further complicated by the lack of appropriate healthcare facilities, professional expertise, and multidisciplinary care. Some of these obstacles are illustrated in the history and outcome of our first case. We believe that the fundamental ethical principles and basic treatment guidelines that we have outlined are compatible with the diverse sociocultural and religious influences in different countries and are universally applicable.

Conclusion

Pregnancy is most likely to coincide with acute lymphoblastic malignancy during younger childbearing years. A delay in initiating therapy poses the greatest risk to the life of both the mother and fetus; therefore, emergent treatment must be provided regardless of the stage of gestation. There is reasonable evidence that standard chemotherapy, if appropriately modified, can be safely administered during even the first trimester of pregnancy with a good outcome for the mother and without long-term harm to the child.

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Disclaimer

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Author Disclosure Statement

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References

1. Voulgaris E, Pentheroudakis G, Pavlidis N. Cancer and pregnancy: a comprehensive review. *Surg Oncol*. 2011; 20(4):e175–85.
2. Hurley TJ, McKinnell JV, Irani MS. Hematologic malignancies in pregnancy. *Obstet Gynecol Clin North Am*. 2005; 32(4):595–614.
3. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer*. 2006;42(2):126–40.
4. Perez CA, Amin J, Aguina LM, et al. Primary mediastinal large B-cell lymphoma during pregnancy. *Case Rep Hematol*. 2012;2012:197347.
5. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *Br J Haematol*. 2013;162(6):792–801.
6. Sandlund JT. Burkitt lymphoma: staging and response evaluation. *Br J Haematol*. 2012;156(6):761–5.
7. Termuhlen AM, Smith LM, Perkins SL, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(7):1229–33.
8. Pereg D, Koren G, Lishner M. Cancer in pregnancy: gaps, challenges and solutions. *Cancer Treat Rev*. 2008;34(4): 302–12.
9. Abadi U, Koren G, Lishner M. Leukemia and lymphoma in pregnancy. *Hematol Oncol Clin North Am*. 2011;25(2): 277–91.
10. Brenner B, Avivi I, Lishner M. Haematological cancers in pregnancy. *Lancet*. 2012;379(9815):580–7.
11. Rizack T, Mega A, Legare R, Castillo J. Management of hematological malignancies during pregnancy. *Am J Hematol*. 2009;84(12):830–41.
12. Shapira T, Pereg D, Lishner M. How I treat acute and chronic leukemia in pregnancy. *Blood Rev*. 2008;22(5): 247–59.
13. Vandenbriele C, Vassou A, Pentheroudakis G, et al. Hematologic malignancies in pregnancy. In: Antica M (Ed). *Acute leukemia—the scientist's perspective and challenge*. Rijeka, Croatia: InTech; 2011; pp. 371–90. Accessed December 20, 2013 from: www.intechopen.com/books/acute-leukemia-the-scientist-s-perspective-and-challenge/hematologic-malignancies-in-pregnancy
14. Horowitz NA, Benyamini N, Wohlfart K, et al. Reproductive organ involvement in non-Hodgkin lymphoma during pregnancy: a systematic review. *Lancet Oncol*. 2013;14(7):e275–82.
15. Shipala EK, Sowayi GA, Kagwiria MP, Were EO. Prevalence of anemia among teenage pregnant girls attending antenatal clinic in two health facilities in Bungoma district Western Kenya. *J Biol Agr Healthc*. 2013;3(6): 67–75.
16. Rizack T, Rosene-Montella K. Special hematologic issues in the pregnant patient. *Hematol Oncol Clin North Am*. 2012;26(2):409–32, x.
17. Han SN, Kesic VI, Van Calsteren K, et al. Cancer in pregnancy: a survey of current clinical practice. *Eur J Obstet Gynecol Reprod Biol*. 2012;167(1):18–23.
18. Weisz B, Schiff E, Lishner M. Cancer in pregnancy: maternal and fetal implications. *Hum Reprod Update*. 2001; 7(4):384–93.
19. Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist*. 2002;7(4):279–87. Erratum in: *Oncologist*. 2002; 7(6):585.
20. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*. 2004;5(5):283–91.
21. Dawes M, Chowienzyk PJ. Drugs in pregnancy. *Pharmacokinetics in pregnancy*. *Best Pract Res Clin Obstet Gynaecol*. 2001;15(6):819–26.
22. Koren G, Lishner M. Pregnancy and commonly used drugs in hematology practice. *Hematology Am Soc Hematol Educ Program*. 2010;2010:160–5.
23. Doll DC, Ringenberg QS, Yarbrow JW. Management of cancer during pregnancy. *Arch Intern Med*. 1988;148(9): 2058–64.
24. Aviles A, Niz J. Long-term follow-up of children born to mothers with acute leukemia during pregnancy. *Med Pediatr Oncol*. 1988;16(1):3–6.
25. Kalter H, Warkeny J. Medical progress. Congenital malformations: etiologic factors and their role in prevention. *N Engl J Med*. 1983;308(8):424–31.
26. Azim HA, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. *Cancer Treat Rev*. 2010;36(2):110–21.

27. Selig BP, Furr JR, Huey RW, et al. Cancer chemotherapeutic agents as human teratogens. *Birth Defects Res A Clin Mol Teratol.* 2012;94(8):626–50.
28. El-Hemaidi I, Robinson SE. Management of haematological malignancy in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2012;26(1):149–60.
29. Bani-Hashem A, Heydarian F, Hiradfar S, Ehteshammanesh H. The effect of L-asparaginase on blood triglycerides, glucose, and albumin levels and coagulation state in ALL patients in pediatric ward. *Avcta Medica Iranica.* 2008; 47(4):275–8.
30. Elliott MA, Wolf RC, Hook CC, et al. Thromboembolism in adults with acute lymphoblastic leukemia during induction with L-asparaginase-containing multi-agent regimens: incidence, risk factors, and possible role of antithrombin. *Leuk Lymphoma.* 2004;45(8):1545–9.
31. Appel IM, Hop WCJ, van Kessel-Bakvis C, et al. L-Asparaginase and the effect of age on coagulation and fibrinolysis in childhood acute lymphoblastic leukemia. *Thromb Haemost.* 2008;100(2):330–7.
32. Adamson RH, Fabro S. Embryotoxic effect of L-asparaginase. *Nature.* 1968;218(5147):1164–5.
33. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. *Ann Oncol.* 2004;15(1):146–50.
34. Gziri MM, Amant F, Debieve F, et al. Effects of chemotherapy during pregnancy on the maternal and fetal heart. *Prenat Diagn.* 2012;32(7):614–9.
35. Gziri MM, Debieve F, De Catte L, et al. Chemotherapy during pregnancy: effect of anthracyclines on fetal and maternal cardiac function. *Acta Obstet Gynecol Scand.* 2012;91(12):1465–8.
36. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. *Blood.* 2008;111(12):5505–8.
37. Conchon M, Sanabani SS, Bendit I, et al. Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: case study. *J Hematol Oncol.* 2009;2:42.
38. Cortes J, O'Brien S, Ault P, et al. Pregnancy outcomes among patients with chronic myeloid leukemia treated with dasatinib. *Blood (ASH Annual Meeting Abstracts).* 2008;112(11):abstract 3230.
39. Chelghoum Y, Vey N, Raffoux E, et al. Acute leukemia during pregnancy: a report on 37 patients and a review of the literature. *Cancer.* 2005;104(1):110–7.
40. Greenlund LJ, Letendre L, Tefferi A. Acute leukemia in pregnancy: a single institutional experience with 17 cases. *Leuk Lymphoma.* 2001;41(5–6):571–7.
41. Matsouka C, Marinopoulos S, Barbaroussi D, Antsaklis A. Acute lymphoblastic leukemia during gestation. *Med Oncol.* 2008;25(2):190–3.
42. Amant F, Van Calsteren K, Halaska M, et al. Long term cognitive and cardiac outcome after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet Oncol.* 2012;13(3):256–64.
43. Aviles A. Hematological malignancies and pregnancy. A brief review. *Rev Recent Clin Trials.* 2009;4(2):131–9.
44. Aviles A, Diaz-Maqueo JC, Torras V, et al. Non-Hodgkin's lymphomas and pregnancy: presentation of 16 cases. *Gynecol Oncol.* 1990;37(3):335–7.
45. Aviles A, Diaz-Maqueo J, Talavera A, et al. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. *Am J Hematol.* 1991;36(4):243–8.
46. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy *in utero*. *Clin Lymphoma.* 2001;2(3):173–7.
47. Aviles A, Neri N, Nambo MJ. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. *Ann Oncol.* 2006;17(2):286–8.
48. Aviles A, Neri N, Nambo MJ. Author's reply: chemotherapy during first trimester of pregnancy. *Int J Cancer.* 2012;132(7):1729.
49. Aviles A, Neri N, Nambo MJ. Hematological malignancies and pregnancy: treat or no treat during first trimester. *Int J Cancer.* 2012;131(11):2678–83.
50. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol.* 2010; 28(4):683–9.
51. Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after *in utero* exposure to chemotherapy: results of an international registry. *Am J Clin Oncol.* 2010;33(3):221–8.
52. Milojkovic D, Apperley JF. How I treat leukemia during pregnancy. *Blood.* 2014;123(7):974–84.
53. Zemlickis D, Lishner M, Degendorfer P, et al. Fetal outcome after *in utero* exposure to cancer chemotherapy. *Arch Intern Med.* 1992;152(3):573–6.
54. Oduncu FS, Kimmig R, Hepp H, Emmerich B. Cancer in pregnancy: maternal-fetal conflict. *J Cancer Res Clin Oncol.* 2003;129(3):133–46.
55. Felice ME, Feinstein RA, Fisher M, et al. Counseling the adolescent about pregnancy options. *Pediatrics.* 1998; 101(5):938–40.
56. Chervenak FA, McCullough LB. An ethically justified practical approach to offering, recommending, performing, and referring for induced abortion and feticide. *Am J Obstet Gynecol.* 2009;201(6):560.e1–6.
57. Chervenak FA, McCullough LB, Knapp RC, et al. A clinically comprehensive ethical framework for offering and recommending cancer treatment before and during pregnancy. *Cancer.* 2004;100(2):215–22.
58. Chervenak FA, McCullough LB, Sharma G, et al. Enhancing patient autonomy with risk assessment and invasive diagnosis: an ethical solution to a clinical challenge. *Am J Obstet Gynecol.* 2008;199(1):19.e1–4.
59. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. *Pediatr Blood Cancer.* 2007;48(3):254–61.
60. Leslie KK, Koil C, Rayburn WF. Chemotherapeutic drugs in pregnancy. *Obstet Gynecol Clin North Am.* 2005;32(4):627–40.
61. Asker C, Norstedt Wikner B, Kallen B. Use of antiemetic drugs during pregnancy in Sweden. *Eur J Clin Pharmacol.* 2005;61(12):899–906.
62. Einarson A, Maltepe C, Navioz Y, et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG.* 2004;111(9):940–3.
63. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood.* 2008;111(9):4477–89.
64. Felice ME, Boulter S, Gotlieb EM, et al. The adolescent's right to confidential care when considering abortion. *Pediatrics.* 1996;97(5):746–51.

65. Rosen EJ. Position paper on mainstreaming adolescent pregnancy in efforts to make pregnancy safer. Geneva: Department of Making Pregnancy Safer, World Health Organization; 2010. Accessed December 24, 2013 from: www.gfmer.ch/SRH-Course-2010/adolescent-sexual-reproductive-health/pdf/WHO-mainstreaming-adolescent-pregnancy-efforts-MPS-2010.pdf
66. UNICEF. The state of the world's children 2007: women and children: the double dividend of gender equality. New York: The United Nations Children's Fund; December 2006.
67. Peccatori FA, Azim HA Jr, Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat*. 2009;115(3):591–4.
68. Zuazu J, Julia A, Sierra J, et al. Pregnancy outcome in hematologic malignancies. *Cancer*. 1991;67(3):703–9.

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