Management of hematological malignancies during pregnancy

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The management of hematological malignancies during pregnancy is a challenging endeavor, which not only requires technical skills and knowledge by the clinicians but also requires sound clinical judgment and compassion, keeping in mind the patient and family preferences and, ultimately, the wellbeing of the neonate. The incidence of hematological malignancies during pregnancy is rare, ranging from 1 in 1,000 to 1 in 10,000 deliveries, impeding the design and execution of large prospective studies. The purpose of this review is to evaluate the limited existing data and make useful suggestions in the management of acute and chronic leukemias, Hodgkin and non-Hodgkin lymphomas, plasma cell myeloma, and other hematological malignancies, such as myelodysplastic syndromes and hairy cell leukemia, during pregnancy. Am. J. Hematol. 84:830–841, 2009. © 2009 Wiley-Liss, Inc.

Introduction

Malignancy affects ~1 in every 1,000 pregnancies and is the second leading cause of maternal death in the United States. However, the incidence is expected to rise with the increasing trend to postpone pregnancy. The majority of cases are solid tumors with hematologic malignancies representing 25% of cancers affecting pregnancy [1]. A low incidence of cases makes prospective trials difficult to execute. Data is often scarce and antiquated; few guidelines for the management of hematological malignancies during pregnancy exist and are mainly based on retrospective data and case reports.

Management of the pregnant patient with a malignancy is a diagnostic, therapeutic, and social challenge requiring a multidisciplinary team approach. The care of the pregnant patient with a malignancy necessitates a difficult balance of trying to cure the mother while minimizing the effects on not only the fetus but future gestations. Hematological malignancies often require prompt therapy. In the pregnant patient this poses a difficult situation of considering the treatment effects on the fetus versus the natural progression of the disease on both the fetus and the mother. Treatment should mimic that of nonpregnant patients as much as possible, taking into consideration the gestational age at presentation, the clinical stage of disease, and the preference of the patient.

Medical Therapy During Pregnancy

Chemotherapy during pregnancy

Whenever possible, treatment should be deferred until the second trimester, after the completion of organogenesis. Chemotherapy in the first trimester can induce a spontaneous abortion or significantly increase the risk of congenital abnormalities. In the first trimester, the risk of congenital malformations is 10% with the use of a single agent and 15–25% with combination therapy [2,3]. Alkylating agents and antimetabolites carry the greatest risk, while vincristine is associated with the lowest risk [3]. Inadvertent therapy given in the first 2 weeks of pregnancy, before fetal circulation has been established, will generally have no effect on the pregnancy (Table I).

After the first trimester, the risk of congenital malformations from chemotherapy is about 3%, which approaches the baseline population risk [4]. Chemotherapeutic effects on pregnancy after the first trimester include low birth weight, intrauterine growth restriction (IUGR), premature birth, stillborn fetus, impaired functional development, myocardial toxicity, and spontaneous abortion [5,6]. Earlier studies have shown that late manifestations of in utero exposure to chemotherapeutic agents may rarely include impaired growth and possibly diminish neurologic and/or intellectual function [7,8]. Toxicities such as anemia, neutropenia, pancytopenia, and alopecia have been observed in newborns [9]. However, longer follow-up and review of existing data have shown that chemotherapy does not have an effect on late neurodevelopment, fertility, or future malignancies in the exposed fetus [10]. Furthermore, a large study investigated the effects of therapy for hematological malignancies on 84 children with a mean follow-up of 18.7 years [11]. The study found no physical, neurological, or psychological abnormalities, and normal cognitive development. In addition, no childhood cancer was reported in the first- or second-generation children [11].

Standard doses of drugs adjusted to continuing weight gain should be used, since studies determining drug levels in utero or fetal tissue are lacking, although the physiologic changes in pregnancy may alter the drug metabolism. These changes include increased plasma volume, decreased serum albumin concentration, enhanced hepatic detoxification of drugs, increased hepatic and renal clearance, and diminished gastric motility. The amniotic sac may be a third space for drugs such as methotrexate and cisplatin. Agents to avoid include aminopterin (rarely used anymore), melphalan, and procarbazine. Methotrexate toxicity has a dose- and trimester-dependent effect [12]. In the first trimester, it is an abortificant often used in the treatment of ectopic pregnancy. High doses of methotrexate are associated with the aminopterin syndrome (i.e., cranial dysotosis, delayed ossification, hypertelorism, wide nasal bridge,

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Conflict of interest: Nothing to report.

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Received for publication 4 May 2009; Revised 8 September 2009; Accepted 12 September 2009

Am. J. Hematol. 84:830–841, 2009.

Published online 16 September 2009 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21547

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TABLE I. Maternal and Fetal Complications Reported with Selected Anticancer Agents Used to Treat Hematological Malignancies

Agent	Use	Major maternal complications	Fetal effects	Pregnancy category
Alkylating agents				
Chlorambucil	CLL, NHL	Myelosuppression	First trimester: A few case reports with no adverse effects, two cases of unilateral renal and ureter agenesis, one case of a retinal defect. Second to third trimester: Several case reports with no adverse effects.	D
Cisplatin	AML, NHL, HL	Myelosuppression; nephrotoxicity; neurotoxicity	First trimester: Two cases with no adverse effects. Second to third trimester: Two cases with no adverse effects; one case with exposure at 26 weeks and delivered 6 days later with neutropenia, hair loss, and hearing impairment.	D
Cyclophosphamide	NHL, CLL, MM, ALL	Myelosuppression	Case series: Twenty-one cases (11 in first trimester) with no anomalies, another series of nine patients (three in first trimester) with no anomalies but one patient treated in all three trimesters delivered an infant with pancytopenia and low birth weight.[a] First trimester: Four cases with digit abnormalities, two with hernias, one single left coronary artery, one stillbirth, one growth retardation, one imperforate anus with rectovaginal fistula, one facial abnormality, developmental delay.[a] Second to third trimester: Few case series of long-term follow-up infants with normal growth and mental development. Low birth weight common side effect. Two infants with pancytopenia with exposure in third trimester.	D
Dacarbazine	HL	Myelosuppression	Case series: Seventeen cases, seven in first trimester, no congenital abnormalities. Second to third trimester: One case exposed in fourth month with no abnormalities.	C
Mechlorethamine	HL	Myelosuppression; infertility	Case series: Six patients, one with first trimester exposure, no congenital anomalies. Series of 13 cases with first trimester exposure: one spontaneous abortion, one elective termination, one infant born with hydrocephalus died 4 hr after birth.[a]	D
Melphalan	MM	Myelosuppression	First trimester: One reported miscarriage.	D
Procarbazine	HL	Myelosuppression; infertility	Case series: Thirteen patients, three received combination chemotherapy, one spontaneous abortion, one elective termination, one with hydrocephalus, died 4 hr after birth. Series of six children, one in first trimester, with no abnormalities. Twenty-six pregnancies: One infant with cleft lip and palate.[a] First trimester: At least six cases only two with normal infants, low birth weight male died after birth found to have atrial septal defect,[a] elective abortion with male infant with markedly reduced malpositioned kidneys, spontaneous abortion at 24 weeks with digital abnormalities,[a] normal infant with multiple hemangiomas. Second to third trimester: No abnormalities described.	D
Anthracyclines				
Daunorubicin	AML, ALL, APML	Myelosuppression; acute and chronic cardiac toxicities	Case series: Nine cases, one with first trimester exposure, no teratogenic effects, two elective terminations, two premature deliveries, two stillbirths (one of which had myocardial necrosis). First trimester: Four patients, two normal, two spontaneous abortions. Second to third trimester: One case of premature delivery, one case of "fetal distress" and transient neonatal marrow suppression.	D
Doxorubicin	HL, NHL	Myelosuppression; acute and chronic cardiac toxicities	First trimester: Nine/ten cases with no adverse outcomes, one case with imperforate anus and rectovaginal fistula.	D
Idarubicin	AML, ALL, APML	Myelosuppression; acute and chronic cardiac toxicities	Five cases all with complications, including one case of IUFD 2 days after infusion for consolidation, another case of IUFD, IUGR, and two cases of cardiomyopathy.[a]	D
Antibiotics				
Bleomycin	HL, NHL	Pneumonitis	Case series: Twenty-three patients (11 in first trimester) with no anomalies.[a] Second to third trimester: Isolated case reports of regimens including bleomycin with no congenital abnormalities. One case of transient leucopenia and neutropenia in a premature infant whose mother received BEP 7–10 days prior to delivery.	D
Antimetabolites				
Cladribine	HCL	Myelosuppression	No cases in literature.	D
Fludarabine	CLL, NHL, MM	Myelosuppression	No cases in literature.	D
Hydroxyurea	AML, ALL, CML, CLL	Myelosuppression	Case series: Nine patients, seven with no adverse effects, one elective abortion of apparently normal fetus, one stillborn without gross abnormalities. Single case report of a normal infant with exposure in all trimesters, which also commented on four other cases: One premature delivery but no congenital defects. Thirty-one cases noted increased risk of IUGR, IUFD, and prematurity, but may have been due to underlying disease.	D
Methotrexate	ALL, NHL	Myelosuppression and Acute renal failure	Case series: Nine patients, five in first trimester, no congenital abnormalities, four low birth weight, one with low birth weight and pancytopenia.[a] Series of eight patients (ten pregnancies) with exposure prior to and during pregnancy: Three spontaneous abortions, two elective abortions, four full-term infants with no abnormalities (all with first trimester exposure). Prospective series of 21 patients, with five exposures during pregnancy (four in first trimester) with no abnormalities. First trimester: At least seven children with aminopterin-type syndrome.	X

TABLE I. (Continued)

Agent	Use	Major maternal complications	Fetal effects	Pregnancy category
			Second to third trimester: One case of severe pancytopenia with exposure in all three trimesters, five cases with no anomalies, one infant with 46 chromosomes but with presence of gaps and a ring chromosome of unknown significance.[a]	
Nucleoside analogs				
Cytarabine	AML, ALL, CML	Myelosuppression	Case series: Case series of nine patients all normal, five in first trimester. Case series of ninepatients, four in first trimester, none with malformations, two with low birth weight, one with severe pancytopenia and low weight. Case series of seven patients, two with low birth weight, one with thrombocytopenia.[a] First trimester: Many case reports with normal infants. One case with low birth weight, digit abnormalities but mother had similar exposure in subsequent pregnancy and delivered a normal infant.[a] One infant with single agent exposure with bilateral microtia with atresia of auditory canals, limb, and digit deformities. Second to third trimester: Three cases with chromosomal abnormalities. One infant with normal phenotype but presence of gaps and a ring chromosome of unknown significance,[a] three cases of IUFD. One infant born with bruising and petechiae, one infant with severe pancytopenia exposed in all three trimesters, one case of severe pancytopenia,[a] two cases of neutropenia with thrombocytopenia.	D
Topoisomerase II inhibitors				
Etoposide	AML, NHL, HL	Myelosuppression, May prolong PT, INR	Case series: Eleven patients, two in first trimester with no congenital abnormalities, one infant born with leucopenia and hearing loss at 27 weeks, transient pancytopenia in infant born at 32 weeks after maternal treatment in third trimester.	D
Vinca alkaloids				
Vinblastine	HL	Myelosuppression	Case series: Ten children, four with exposure during first trimester, none with abnormalities. Series of 26 patients, one infant born with hydrocephalus with exposure at Week 3, one infant with cleft palate exposed during first trimester.[a] Six patients with no congenital anomalies abnormalities. First trimester: More than 15 cases reported, one spontaneous abortion with digital abnormalities, one low birth weight infant died shortly after birth from small secundum atrial defect.[a] Second to third trimester: More than ten cases reported with no abnormalities.	D
Vincristine	HL, NHL, ALL	Neurotoxicity	Case series: No anomalies observed in 28 children, 12 women treated in the first trimester. Series of nine patients, five treated during first trimester, had no anomalies: four with low birth weight, one with severe neutropenia and low birth weight.[a] Series of seven patients, three during second or third trimester, no congenital abnormalities. Series of 26 pregnancies, one cleft lip and palate.[a] Series of 13 patients with first trimester exposure, out of four pregnancies there was one normal live birth, one spontaneous abortion, one elective termination, and one hydrocephalus, died 4 hr after birth.[a] First trimester: Two malformed infants reported: one low birth weight infant died shortly after birth from small secundum atrial defect and one elective abortion with markedly reduced malformed kidneys.[a] Two other malformed infants were reported in a cases series.[a] One healthy infant treated after 22nd week with 46 chromosomes with the presence of gaps and a ring chromosome of unknown significance.[a] One case of severe pancytopenia[a] and one case of transient severe bone marrow suppression[a] (felt to be due to mercaptopurine exposure). One case of IUFD.	D
Monoclonal antibodies				
Ibritumomab	NHL	Infusion-related reactions; myelosuppression	Contraindicated in pregnancy due to prohibitive fetal radiation exposure.	D
Rituximab	NHL	Infusion-related reactions; myelosuppression	Few reports show safety in all trimesters. Transient B-cell depletion reported followed by full immunologic recovery and normal response to vaccines.	C
Tositumomab	NHL	Infusion-related reactions; myelosuppression	Contraindicated due to prohibitive fetal radiation exposure.	X
Tyrosine kinase inhibitors				
Dasatinib	CML	Fluid retention	Case series: Eight patients, three elective terminations, two spontaneous abortions, three healthy deliveries, one unknown outcome.	D
Imatinib	CML	Fatigue; fluid retention	Case series: One hundred and eighty patients, 103 with first trimester exposure, 38 exposed in all three trimesters, 125 with available data. Fifty percent delivered normal infants, 35 elected termination (three for known congenital abnormalities). Twelve infants born with abnormalities: Three with similar defects including exomphalos, cardiac, and renal anomalies.	D
Miscellaneous				
All-trans retinoic acid (ATRA)	APML	Hemorrhage DIC	First trimester: Eighty-five percent risk of teratogenicity, including severe neurological and cardiovascular complications. Increased rate of miscarriage.[a] Second to third trimesters: No congenital abnormalities reported.	D
Asparaginase	ALL	Allergic reactions; hypofibrinogenemia	Case series: Nine cases,[a] four in first trimester, with no congenital abnormalities, one case of transient oligohydramnios, meconium, and low birth weight, and one infant with normal phenotype but presence of gaps and a ring chromosome of unknown significance.	C
Bortezomib	MM	Neuropathy; hypotension	No cases in literature.	D

micrognatia, and ear anomalies) [9,13]. Most experts recommend against the use of methotrexate in pregnancy unless no acceptable alternative exists.

Supportive therapy during pregnancy

The use of supportive therapy should be the same as for the general population. Antihistamines, ondansetron, phenothiazines, metoclopramide, and corticosteroids have fairly good safety profiles in pregnancy [14].

Antiemetics. A large retrospective study of 3,458 patients exposed to metoclopramide during their first trimester found no increase in adverse outcomes on the fetus or pregnancy when compared to pregnant patients who did not receive metoclopramide [15]. Ondansetron, a 5-HT_3-serotonin antagonist, has been reported to be safe in pregnancy. Four cases were exposed to ondansetron during first, second, and/or third trimesters; there were no fetal adverse outcomes with a highly efficacious control of hyperemesis in the mother [16–19]. The only prospective trial of ondansetron included 176 women exposed in the first trimester and did not appear to be associated with an increased risk of major malformations above baseline, but the sample size was felt to be limited [20]. Granisetron has been studied prospectively to prevent nausea and vomiting during cesarean section and has been shown to be safe and effective in this setting [21]. There is not enough data to support the use of other 5-HT_3-serotonin antagonists or aprepitant.

Growth factors. Erythropoietin does not cross the placenta and its use is felt to be safe in pregnancy [22]. Granulocyte colony-stimulating factor use in pregnancy has been reported in a registry series of 20 patients with severe chronic neutropenia with a median dose of 2.7 mcg/kg/day administered daily or every other day during all three trimesters with an average duration of three trimesters. These data, although limited, did not reveal an increase in adverse congenital abnormalities or fetal death compared to pregnant patients that did not receive the drug [23].

Bisphosphonates. Although the use of bisphosphonates during pregnancy has not been evaluated prospectively, a recent literature search including 51 patients exposed to bisphosphonates shortly prior to conception or during pregnancy did not find evidence of skeletal abnormalities or malformations in the products of the exposed mothers [24].

Leukapheresis. Leukapheresis has been used in both acute and chronic leukemia to rapidly reduce high white blood cell counts in patients with impending vascular occlusion. Experience with leukapheresis during pregnancy is limited to only a handful of cases used to treat both chronic and acute leukemias [25–31]. In general, the therapy was tolerated well by the mother and the fetus. Although experience is limited, leukapheresis may be used as a short-term temporizing measure when no other options exist or in patients refusing other therapies during pregnancy.

Management of Lymphoma During Pregnancy

Whenever possible, diagnosis should be made with an excisional biopsy of a lymph node, a procedure that is easy to perform and has not shown increased morbidity or mortality to the mother or the fetus [32,33]. Staging should be done with a posterior/anterior chest X-ray with abdominal shielding, and routine blood work, including complete blood count, erythrocyte sedimentation rate, serum creatinine, and liver enzymes, including lactate dehydrogenase and alkaline phosphatase [34]. However, serum alkaline phosphatase is significantly elevated in the third trimester and may not be useful. A pathologic placental evaluation after delivery should be done routinely to assess the need for appropriate staging and therapy in the neonate [1]. A bone

TABLE I. (Continued)

Agent	Use	Major maternal complications	Fetal effects	Pregnancy category
Interferon alpha	MM, HCL, CML	Flu-like illness; fatigue; infertility	Forty cases documented in literature, eight in first trimester, only one case of fetal malformations with concurrent use of hydroxyurea.	C
Lenalidomide	MM, MDS	Myelosuppression; thrombosis	Perinatal risks based on experience with thalidomide.	X
Thalidomide	MM	Neuropathy; thrombosis	Severe malformations include defects of the limbs, axial skeleton, head and face, eyes, ears, tongue, teeth, central nervous, respiratory, cardiovascular, and genitourinary systems, and the gastrointestinal tract with risk of congenital malformations between 20 and 50%.	X

Table adapted and modified from http://www.motherisk.org/women/cancerCategory.jsp?category_id=27.

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; BEP, bleomycin, etoposide, cisplatin; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DIC, disseminated intravascular coagulation; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; IUFD, intrauterine fetal demise; IUGR, intrauterine growth retardation.

[a] Multiple drug regimen used.

Pregnancy category interpretation: A: Controlled studies show no risk; adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus. B: No evidence of risk in humans; either animal findings show risk (but human findings do not) or, if no adequate human studies have been done, animal findings are negative. C: Risk cannot be ruled out; human studies are lacking and animal studies are either positive for fetal risk or lacking as well; however, potential benefits may justify the potential risk. D: Positive evidence of risk; investigational or postmarketing data show risk to fetus; nevertheless, potential benefits may outweigh the risk. X: Contraindicated in pregnancy; studies in animals or humans, or investigational or postmarketing reports have shown fetal risk, which clearly outweighs any possible benefit to the patient.

marrow biopsy is recommended for non-Hodgkin lymphoma (NHL) and only in patients with B symptoms or cytopenias in Hodgkin lymphoma (HL). Intrabdominal disease can be evaluated with noncontrast MRI or ultrasound [35,36]. PET and gallium have not proven to be safe in pregnancy [37]. Bone scans are generally not recommended unless there are no other means of detecting bone metastases and results would change management. Baker et al. described about a series of three pregnant patients with breast cancer who received a modified bone scan to reduce fetal exposure with normal outcomes in the offspring. The authors suggest using 10 mCI rather than 20 mCI and doubling the imaging time to reduce fetal exposure [38]. A Foley catheter should be placed while hydrating the patient to promote rapid washout of the excreted radiopharmaceutical from the patient's bladder. On the other hand, MRI has a diagnostic accuracy of 91% for the detection of bone metastases in hematological malignancies [39].

Delivery should be delayed until fetal maturity is achieved, without compromising the health of the mother or fetus. If bleomycin was used during pregnancy, it has been suggested that the women should not receive oxygen during delivery not to exacerbate possible pulmonary toxicity [40]. A cesarean delivery is not warranted unless otherwise indicated, because staging laparotomy is no longer recommended. Delivery should be planned no less than 2 weeks but ideally 3–4 weeks after chemotherapy to allow for maternal and fetal blood count recovery and complete chemotherapy metabolism by the fetus and placenta. A full-staging assessment should be performed postpartum in all patients, usually with a PET-CT; 18F-FDG can cross the placenta and is concentrated in breast tissue and in breast milk [41]. The patient should not hold the infant for 24 hr after the PET scan to decrease radiation exposure of the newborn. If breastfeeding, the patient should discontinue giving the baby breast milk for 72 hr after a PET scan. It is recommended that patients treated for cancer wait 1 or 2 years after the completion of chemotherapy before conceiving, as this is the most likely period of disease recurrence. In lymphoma patients felt to have a high likelihood of cure, 1 year may be adequate.

Hodgkin lymphoma

HL is more commonly seen during pregnancy than NHL because the peak incidence of HL coincides with the reproductive years. HL affects one in 1,000–6,000 pregnancies [42] and concurrent pregnancy has been identified in 3.2% of all patients with HL [43]. HL is more commonly seen in women with lower parity and advanced maternal age, but the clinical behavior and prognosis are similar to those of nonpregnant women [44]. Pathologically, the majority of cases present with nodular sclerosing HL, which is also the most common histology seen in women younger than 40 years [45]. The largest study to date, consisting of 48 pregnant women matched to nonpregnant controls with HL, showed a median age of 26 years without difference in stage distribution at diagnosis [46]. See Fig. 1 for an algorithmic approach to the management of HL in pregnancy.

Early-stage HL. In general terms, treatment of early-stage HL should and can be deferred until after the second trimester [34,47]. In fact, more than 50% of patients can continue pregnancy to term without treatment [48]. Thus, if an early-stage HL diagnosis is made early in pregnancy, a watchful waiting approach is reasonable. If treatment is required, it is usually possible to control the lymphoma with single-agent chemotherapy, such as vinblastine or anthracyclines, allowing the pregnancy to go to term [34,47,48]. The combination of doxorubicin, vincristine, bleomycin, and

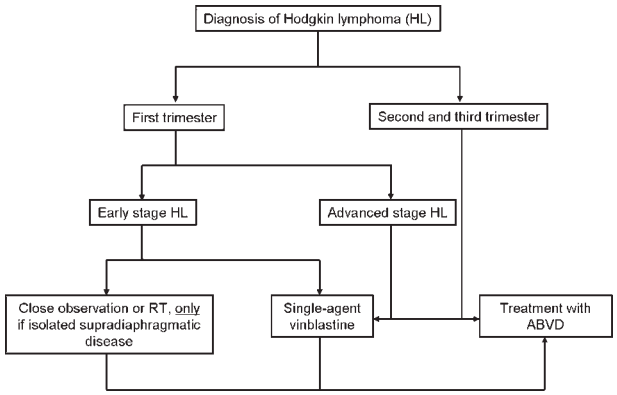

Figure 1. Proposed management of Hodgkin lymphoma during pregnancy.

dacarbazine (ABVD) is the most frequently employed regimen in the US and is considered the standard of care [49]. Recently, a study about a series of 17 patients treated over the past 21 years was published favoring the use of single-agent vinblastine; 11 patients required no treatment during pregnancy and 6 required single-agent vinblastine to control disease until delivery. This series found a greater than 75% response rate to single-agent vinblastine at doses of 6 mg/m^2 used in treatment-naïve patients at intervals of several weeks or longer with minimal toxicity to mother and child. All 17 women treated delivered normal infants now ranging in age from 2 to 21 years [48]. Several other articles report the use of single agent vinblastine in the first trimester with no adverse effects on the fetus (except for one case of fetal syndactyly in a child whose mother also received oral cyclophosphamide during all three trimesters) and favorable disease response [50]. Patients who progress despite vinblastine can be treated with ABVD during the second or third trimester.

Several studies have documented the efficacy of radiation for early-stage HL during pregnancy [43,45,47]. Radiation should be reserved for cases in which it is absolutely necessary and extreme precaution should be undertaken to limit the whole body fetal dose to less than or equal to 0.1 Gy and to protect the uterus by using 10 half-value layer shielding [5]. Prior to treatment, the maximal dose to the fetus should be calculated and then monitored throughout treatment [51]. The aim is for partial rather than definitive therapy until after delivery. Early stage supradiagphragmatic disease such as isolated cervical or axillary sites may be treated with involved-field radiation therapy [43,52]. Mediastinal sites or mantle field irradiation are feasible in pregnant women with early stage HL during the second and third trimester, if special attention is paid to shielding and radiation delivery techniques [43,52]. Healthy offspring was seen in all the cases treated with mediastinal irradiation for supradiaphragmatic HL, with midfetal doses of less than 0.05 Gy [43,52]. However, other studies using a dummy have shown that the embryo is exposed to doses higher than 0.1 Gy, despite appropriate shielding [53]. With recent advances in radiation oncology techniques, especially smaller portal sites, the risk is likely to be lower than previously reported [51].

Treatment delay may also be considered in limited clinical stage IA or IIA HL presenting during the second or third trimester, stable nonurgent HL diagnosed after 20 weeks gestation, or clinically accessible sites of disease that can be easily monitored [5,42]. Accumulating but still limited data have shown the feasibility and safety of administering

full-courses of chemotherapy during the second and third trimesters of pregnancy.

Advanced-stage or relapsed HL. If advanced HL is diagnosed during the first trimester, termination of the pregnancy should be considered followed by appropriate staging and adequate doses of combination chemotherapy. Treatment should not be delayed during pregnancy if patient presents with symptomatic (i.e. B symptoms), bulky, subdiaphragmatic, or progressive HL after the first trimester. ABVD is also the most popular chemotherapeutic regimen in this setting and is considered the standard of care [54]. There is no available data on the use of more intensive regimens such as Stanford V or BEACOPP in pregnancy. Patients who are able to deliver without treatment should be fully restaged after delivery. Women who received treatment during pregnancy can no longer be staged accurately and should complete a full course of combination chemotherapy [48].

Relapsed HL during pregnancy can be treated with chemotherapy, if the patient has been previously treated only with radiotherapy. Salvage chemotherapy may be effective to permit the pregnancy to go to term. In some cases, if a relapse occurs late in pregnancy, observation may be appropriate. If high-dose chemotherapy followed by hematopoietic stem cell rescue is needed and delivery cannot be planned within a reasonable time, termination of the pregnancy would be necessary. Because of the lack of data in regards of the management of relapsed HL during pregnancy, the above recommendations are based on individual opinion.

Non-Hodgkin lymphoma

NHL occurs only rarely in pregnancy with ~100 cases reported in the literature. The occurrence of NHL during pregnancy is expected to increase due not only to the current trend to postpone pregnancy, but the increasing incidence of HIV-associated lymphoma in developing countries [34]. The most common NHL subtypes seen in pregnancy are of an aggressive histology, such as diffuse large B-cell lymphoma (DLBCL). However, other histological variants have also been reported, including Burkitt lymphoma [55–65], follicular lymphoma [59,66], MALT lymphoma [67,68], mycosis fungoides [69,70], anaplastic large cell lymphoma [71,72], hepatosplenic T-cell lymphoma [73], NK/T-cell lymphoma [74], adult T-cell leukemia/lymphoma [75], and subcutaneous panniculitis-like T-cell lymphoma [76,77]. Presenting symptoms of NHL can be unusual during pregnancy leading to delays in diagnosis [78]. A high incidence of involvement of the breast [61,63,79–84], uterus [55,85], cervix [86], and ovaries [65] by NHL has been reported during pregnancy. Involvement of the products of conception by malignancy is very rare; NHL has been reported to involve the products of gestation, including the fetus, in four cases, three of T-cell and one of B-cell subtype [87–90]. See Fig. 2 for an algorithmic approach to the management of NHL in pregnancy.

Indolent NHL. Indolent subtypes of NHL include follicular and MALT lymphoma and mycosis fungoides, between others, and are characterized by a protracted clinical course, in most cases lasting years without necessitating therapy. Thus, an initial expectant approach in pregnant women diagnosed with indolent NHL is reasonable. One patient was inadvertently exposed to rituximab in the first trimester for the treatment of follicular lymphoma; disease control was achieved without adverse fetal outcomes [66]. The initial treatment of gastric MALT lymphoma, which is strongly associated to *Helicobacter pylori* infection, requires antibiotic therapy with almost negligible risk for mother and child.

Although rare, the few cases of indolent NHL presenting with isolated cervical or axillary lymphadenopathy may undergo radiation therapy with appropriate abdominal shielding. The use of radiolabeled monoclonal antibodies such as ibritumomab and tositumomab, both FDA-approved in the management of indolent B-cell NHL, is contraindicated during pregnancy due to prohibitive fetal radiation exposure.

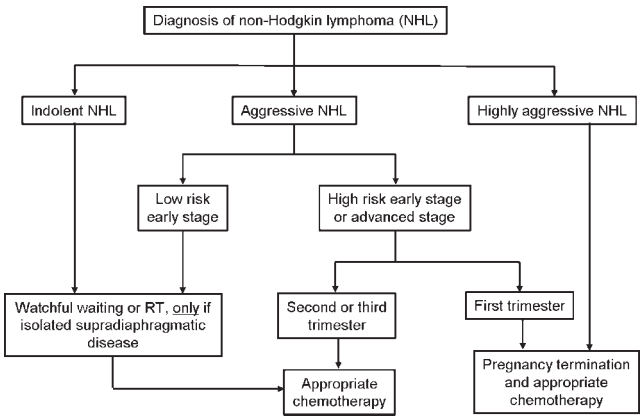

Figure 2. Proposed management of non-Hodgkin lymphoma during pregnancy.

Aggressive NHL. Treatment during the first trimester is complex and patients with aggressive disease should be counseled regarding therapeutic abortion, taking into consideration the risk of staging, chemotherapy, and radiation therapy [91]. Close observation or radiation therapy [92,93] during the first trimester could be considered in those patients presenting with early stage disease, low-volume disease, no B symptoms, and low international prognostic index (IPI) score. The IPI score is the most widely used prognostic tool for risk-stratification in aggressive NHL [94]. Patients with bulky disease or poorer prognostic indicators, such as high IPI score, B symptoms, or high Ki-67 in their biopsies should be treated immediately after pregnancy termination. Beyond the first trimester, standard chemotherapy should be instituted despite potential fetal risks due to the poor prognosis of aggressive NHL without therapy.

As the majority of NHL in pregnancy is DLBCL, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the recommended treatment in the second and third trimester [68,77,84,90,95,96]. Similar anthracycline and cyclophosphamide-containing regimens are routinely used in pregnant women with breast cancer during the second and third trimesters with minimal risk to mother or fetus [9]. Although the use of CHOP does not seem to affect fetal development when used during the first trimester [9,97], the mother should understand the potential risk of fetal malformations associated with chemotherapy during this period [98]. The combination of rituximab and CHOP (R-CHOP) is considered the standard of care for the treatment of DLBCL; more recent data also support its use in pregnant women with aggressive B-cell lymphoma [99–102]. Few non-oncological case reports show that rituximab use is safe in pregnancy, even during the first trimester, and only transient B-cell depletion has been reported in neonates exposed to rituximab, which is followed by full immunological recovery and normal response to vaccines [103–105].

Radiation therapy, which is used for the treatment of early stages of DLBCL or after chemotherapy in cases presenting with bulky disease, should be delayed until after delivery; if given after chemotherapy, it should be preferably given within 9 weeks of the last cycle of chemotherapy [78,106].

Highly aggressive NHL. The development of Burkitt and Burkitt-like lymphoma during pregnancy accounts for

most of the cases of highly aggressive NHL reported in the literature [55–65]. There is a suggestion that these lymphomas are especially aggressive during pregnancy, although the pathogenetic reasons for this behavior are not understood and could also be explained by the use of insufficient therapy (i.e. CHOP). Because of the aggressiveness of these conditions and the poor prognosis they carry if left untreated, pregnancy should be terminated followed by institution of highly intensive combination chemotherapy with or without rituximab. Methotrexate-containing regimens, such as HyperCVAD, carry a high risk of teratogenicity when used during the first trimester and profound fetal myelosuppression when used during the second or third trimesters has been reported [11]. Methotrexate is an essential component of these regimens and high levels are needed to provide adequate levels within the CNS, which is considered a sanctuary of disease in Burkitt lymphoma.

Management of Plasma Cell Myeloma During Pregnancy

Plasma cell myeloma (PCM) is a disease of older individuals, and although several cases have been reported in individuals younger than 40, these account for ~2% of all cases [107]. Furthermore, with an incidence of PCM of three to four cases per 100,000, the experience of managing PCM in pregnancy is rather limited to a handful of cases reported in the literature [108–121]. The offspring of the reported cases appear unaffected by the maternal disease. Usually, PCM tends to present as an indolent disease allowing for an expectant approach [108,109,112,114,116 119,120]. In cases that present with more aggressive disease, immediate delivery [121], pregnancy termination [118], or medical therapy with dexamethasone [117] should be considered according to the patient's condition and preference. In patients with extensive pelvic or spinal involvement, cesarean section was used to avoid further trauma from the stress of labor and a vaginal delivery [111,116,121]. Although the use of interferon alpha [115] and low-dose cyclophosphamide [111] has been reported, there is not clear evidence that these therapies are beneficial in PCM. Thalidomide and lenalidomide are highly teratogenic and their use in pregnancy is absolutely contraindicated. Hematopoietic stem cell transplantation is also contraindicated in pregnant women.

Management of Leukemia During Pregnancy

Leukemia in pregnancy is rare affecting one per 75,000–100,000 pregnancies annually [122,123]. The majority of cases are acute leukemias of which two-thirds are acute myeloid leukemia (AML) and one-third acute lymphocytic leukemia (ALL). Chronic myeloid leukemia (CML) accounts for about 10% of all pregnancy-associated leukemias, and chronic lymphocytic leukemia (CLL) is extremely rare [10,123].

Acute leukemia can affect perinatal outcome despite treatment as it can affect both the pregnancy and the fetus. Problems include maternal anemia, disseminated intravascular coagulation [124], placental effects of leukemic cells, decreased blood flow, and decreased exchange of oxygen and nutrients [125,126]. Only one case of vertical transmission of AML from mother to infant has been reported in the literature [127]. Adverse outcomes include induced and spontaneous abortion, preterm labor, IUGR, and stillbirth [7,128,129]. Pregnancy may be associated with anemia and leukocytosis, which could theoretically delay the diagnosis of leukemia, but there has been no published evidence to suggest this [10]. A bone marrow biopsy can safely be performed in pregnancy [32].

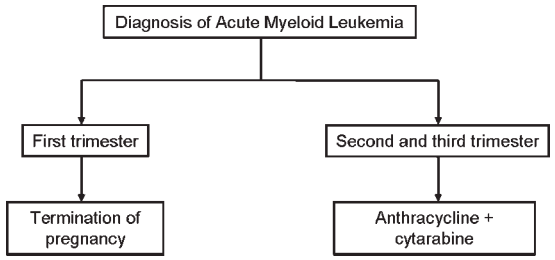

Figure 3. Proposed management of acute myeloid leukemia during pregnancy.

Acute leukemias

Acute leukemia in pregnancy presents complex ethical and therapeutic dilemmas that should involve a multidisciplinary team including a medical oncologist, maternal-fetal medicine, neonatologist, geneticist, and social worker. Acute leukemia in pregnancy requires immediate treatment regardless of gestational age as delays or modification in therapy can adversely affect the maternal prognosis [130]. If untreated, maternal death can occur within 2 months.

The rarity of acute leukemia in pregnancy is emphasized by the paucity of available data. The largest published single institution experience of acute leukemia in pregnancy is from the Mayo Clinic; from 1962 to 1999, 17 cases of acute leukemia in pregnancy were treated with a variety of outcomes [131]. An additional retrospective study of 37 patients from 13 French centers was performed from 1988 to 2003 [132]. Combinations of vincristine, doxorubicin, daunorubicin, idarubicin, cytarabine, cyclophosphamide, asparaginase, mercaptopurine, prednisone, methotrexate, mitoxantrone, and all-trans-retinoic acid (ATRA) have been used during all trimesters. A review of 152 patients with ALL (63 cases) and AML (89 cases) found six (4%) neonates with congenital abnormalities, 12 (8%) with IUGR, 11 (7%) fetal demises, and 2 (1%) neonatal deaths [9].

Acute myeloid leukemia. In the majority of cases, AML is diagnosed in the second and third trimesters [129]. The standard regimen of cytarabine and an anthracycline is recommended for induction. Cytarabine use in pregnancy is limited and a review of 93 cases of first trimester exposure alone or in combination with other chemotherapeutic agents showed four cases of limb malformations and in the second and third trimester was associated with transient cytopenias in 5 cases, intrauterine fetal death in 6 cases, IUGR in 12 cases, and 2 neonatal death from sepsis and gastroenteritis [9]. Cytarabine use in the first trimester is not advocated and termination is strongly preferred. Daunorubicin is the anthracycline of choice in pregnancy [1,9,133,134]. Although only three cases of fetal cardiac toxicity have been documented with anthracycline use, fetal cardiac function should be monitored during pregnancy in addition to limb formation with cytarabine use [135].

Consolidation with the use of lower dose cytarabine and anthracyclines is preferred over topoisomerase inhibitors where experience is extremely limited. Termination of pregnancy in relapsed AML is recommended, because treatment requires high-dose chemotherapy, stem cell transplantation, or experimental drugs, which cannot be given safely in pregnancy. See Fig. 3 for an algorithmic approach to the management of AML in pregnancy.

Acute promyelocytic leukemia. Acute promyelocytic leukemia (APML) in pregnancy is rare [45]. However, APML carries an increased risk of DIC, which can be exaggerated by pregnancy and/or the use of conventional chemotherapy [136]. The treatment of APML was revolutionized by the introduction of ATRA. ATRA decreases the

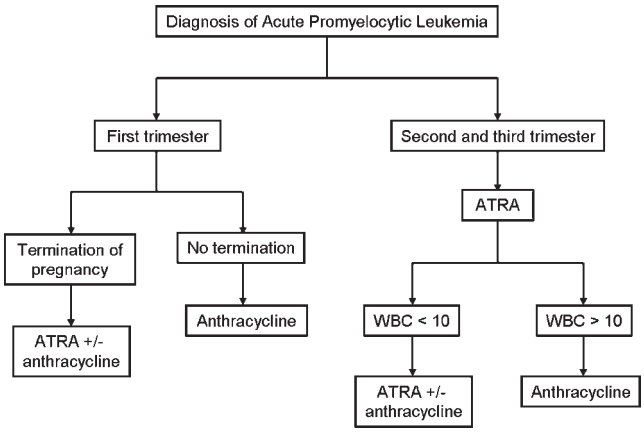

Figure 4. Proposed management of acute promyelocytic leukemia during pregnancy.

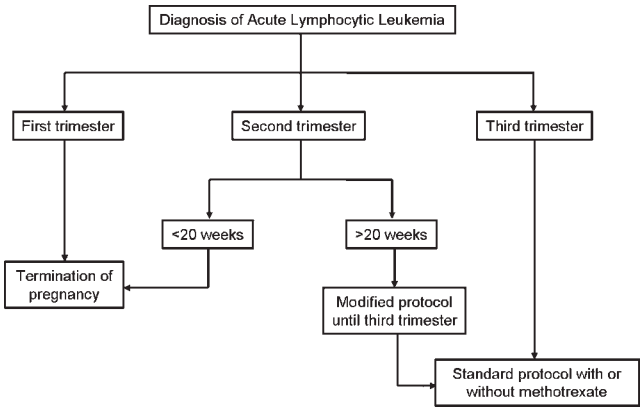

Figure 5. Proposed management of acute lymphocytic leukemia during pregnancy.

risk of DIC and increases the cure rate to more than 70%. Use of ATRA in pregnancy was first published in 1994 and since then there have been 29 case reports of ATRA use in pregnancy [136–139]. ATRA given in the first trimester carries an 85% risk of teratogenicity, including severe neurological and cardiovascular complications, and together with chemotherapy is associated with an increased rate of miscarriage [10]. ATRA, alone and in combination, given in the second and third trimesters has generally shown favorable outcomes in the mother and fetus.

In the first trimester, a therapeutic abortion is recommended after a detailed discussion with the patient and when clinically feasible. ATRA should be initiated with or without the use of an anthracycline if pregnancy termination is planned. If termination is not planned, an anthracycline alone should be used in the first trimester [10].

In the second and third trimester, clinical decisions regarding treatment should be weighed against the gestational age, presence of DIC, and the leukocyte count. ATRA should be initiated as soon as the disease is confirmed. If the leukocyte count is less than 10 k/mm^3, ATRA with or without an anthracycline is recommended. If leukocyte count is greater than 10 k/mm^3, an anthracycline alone is recommended to decrease the risk of differentiation syndrome [140]. Frequent hematological and molecular monitoring is recommended for the mother. Chemotherapy should be avoided 3–4 weeks prior to delivery to reduce maternal and fetal cytopenias. Vaginal delivery after 32 weeks should be attempted, if feasible. Arsenic trioxide is teratogenic and contraindicated in pregnancy. See Fig. 4 for an algorithmic approach to the management of APML in pregnancy.

Acute lymphocytic leukemia. ALL is rare among adults and only 21 cases of ALL in pregnancy have been published in the literature with poor follow-up data in many patients [131,141–145]. Because of its aggressive nature, prompt chemotherapy is recommended once the diagnosis of ALL is made. Recently, studies about two cases of ALL diagnosed in the third trimester were published with delivery at 32.4 weeks due to IUGR in one case and at 33 weeks due to preterm premature rupture of the membranes in the other [141,144]. Despite both infants suffering respiratory distress after delivery, both were reportedly doing well several months after delivery. Both patients received induction chemotherapy that included prednisolone, vincristine, daunorubicin, and L-asparaginase.

Methotrexate, a crucial component of most ALL regimens, is highly teratogenic and an abortifacient in the first trimester. Intrathecal methotrexate use has only been reported in one case [144]. Termination is suggested followed shortly thereafter by chemotherapy for patients prior to the 20th week of gestation. After the 20th week, a modified protocol that does not use methotrexate may be used until the third trimester. Cytarabine, cyclophosphamide, *Vinca* alkaloids, L-asparaginase, anthracyclines, and steroids have all been used in pregnancy. In the third trimester, treatment protocols similar to nonpregnant patient should be followed [145]. Whenever possible, delivery should be planned when the patient is not cytopenic, usually after the 32nd week of gestation. See Fig. 5 for an algorithmic approach to the management of ALL in pregnancy.

Chronic leukemias

Chronic myelogenous leukemia. Only 10% of cases of CML occur in women of childbearing age [146]. Imatinib mesylate, a tyrosine kinase inhibitor, has revolutionized the treatment of CML. Imatinib, however, is felt to be teratogenic in animal models and contraception is recommended with its use. Use of imatinib in the treatment of CML during pregnancy had been limited until a recent publication by Pye et al. of 180 women exposed during pregnancy [147]. Outcome data were available for 125 of these women; 50% delivered normal infants and 28% elected termination (three for known abnormalities of the fetus). Of 12 infants born with abnormalities, 3 had similar complex combinations of defects leading the authors to conclude that although the majority of patients had normal outcomes there remains a risk that exposure may result in serious fetal malformations. Data on prognosis with cessation of imatinib is limited to only a small number of patients with rapid recurrence of disease in many patients but remission achievable in most with reinitiating imatinib [148,149]. Pye also presented follow-up on 10 patients who had discontinued imatinib due to pregnancy [147,150]. Nine of the 10 patients had a complete hematological response (CHR) prior to pregnancy. Five out of the nine patients lost their CHR while off imatinib, but all were able to achieve CHR within 18 months.

Eight patients have become pregnant on dasatinib: three had induced abortions, two had first-trimester spontaneous abortions, and three delivered. Among the deliveries were a healthy infant at term, a cesarean section for unknown reasons at 7 months with a reported healthy infant, and the third case had not delivered at the time of publication, but had a healthy pregnancy [151]. Given the limited data, it is recommended that patients on dasatinib avoid pregnancy.

Prior to the era of imatinib, interferon alpha was the treatment of choice for patients ineligible for transplant.

Interferon alpha is thought to only minimally cross the placenta due to its high molecular weight [152]. Animal studies have not shown evidence of teratogenicity, but one study in *Rhesus* monkeys showed an increased incidence of abortion; however, doses were several fold greater than those used to treat CML in humans [153]. Fertility may be adversely affected as interferon causes a decrease in serum estradiol and progesterone [154]. Interferon used as monotherapy in pregnancy does not appear to be mutagenic. There have been 40 cases of interferon use in pregnancy for a variety of hematological disorders [CML, PCM, hairy cell leukemia (HCL), and essential thrombocytosis], including eight cases of first trimester use [152,153,155,156]. The only case of fetal malformations was seen when interferon was used concurrently with hydroxyurea.

Hydroxyurea, an antineoplastic drug that inhibits DNA synthesis, is a small molecule capable of crossing the placenta. Its use in pregnancy has been documented in 54 cases during various trimesters: 8 patients terminated pregnancy, 42 live births (10 premature, 1 IUGR, 1 preeclampsia, and 1 IUGR with multiple anomalies), and 4 uterine demises [157]. The largest study looking at 31 cases from a single institution noted an increased risk of IUGR, uterine demise, and prematurity, but felt these complications may have also been due to the underlying disease they were used to treat [158].

Patients newly diagnosed with CML in pregnancy should be treated with interferon until after delivery. For patients on imatinib who become pregnant a detailed discussion should ensue of continuing the drug with the possible risk of congenital anomalies versus the risk of disease progression or resistance to imatinib or other tyrosine kinases if imatinib were discontinued. Patients in the second or third trimester who are unable to tolerate interferon may be treated with hydroxyurea or possibly imatinib.

Only one case of accelerated phase CML in pregnancy has been published [150]. Imatinib has been used to treat CML in accelerated or blastic phases with high response rates and can be offered to patients in the second or third trimester with close follow-up of the mother and fetus. Resistant CML requires stem cell transplant and would necessitate termination of the pregnancy.

Chronic lymphocytic leukemia. CLL, predominantly a disease of the elderly, is more common in men and is rare in pregnancy. Its course is usually indolent. Five cases of CLL in pregnancy have been reported in the literature [25,159–162]. Two cases were complicated by infections during pregnancy: one a urinary tract infection and the other recurrent respiratory tract infections. One patient with Stage IV disease and leukocytosis over 100 k/mm^3, who refused chemotherapy, was successfully treated with three courses of leukapheresis at weeks 25, 30, and 38 of gestation [25]. One case report of a patient on chlorambucil and allopurinol was found to be pregnant at 20 weeks of gestation at which time the medications were discontinued [159]. The patient developed preeclampsia at 35 weeks but delivered a healthy infant via cesarean section. At the time of the article was published she did not require additional treatment for her CLL. Two other cases of chlorambucil in pregnancy have been reported; one resulted in bilateral renal agenesis and the other in a normal infant [163,164]. Two cases of placental invasion have been described but did not involve the fetus [161,162]. In general, treatment of pregnant patients with CLL should be delayed until after delivery with close monitoring. If progression of disease occurs cytoreduction with leukapheresis should be first line. There is not enough data to recommend the use of chlorambucil in pregnancy. Fludarabine use has not been reported in pregnancy and antimetabolites are associated with a higher risk of teratogenesis. Autoimmune complications may be treated with corticosteroids similar to nonpregnant patients.

Other Hematological Malignancies

Hairy cell leukemia

From the cases of HCL found in the literature, one case was managed expectantly [165], two cases were treated with interferon alpha [153], two cases underwent splenectomy during pregnancy [166,167], and one case opted for termination of pregnancy [168]. All neonates were healthy and delivered without complications; however, long-term data is not available. There is no data on the use of cladribine during pregnancy.

Myelodysplastic syndromes

A fistful of cases of myelodysplastic syndrome (MDS) and pregnancy was identified [169–179], and in general terms fewer than 40 cases have been reported. In the larger series [173,176–178], patients tend to have lower risk disease and managed with red blood cell and platelet transfusions, as needed. Few cases have reported the use of erythropoietin in MDS during pregnancy [175]. The risk of transformation into AML has not been studied extensively, but the rate of transformation varies between 25 and 60% [176,177]. However, an Italian study with a follow up of 9 years did not report transformation into AML [178]. In patients with pre-existing MDS who want to become pregnant, the international prognostic score system and other prognostic factors should be used to frame discussions with such patients [177].

Conclusion

In general, the majority of pregnant women diagnosed with a malignancy have good pregnancy outcomes and their prognosis does not differ significantly from nonpregnant women. Care of a pregnant patient with a malignancy should be individualized and a multidisciplinary team should be established with a treatment plan taking into account the patient preference and the currently available therapies. Chemotherapeutic agents should be chosen based on the most extensive evidence at the time. Chemotherapy should be delayed until the second trimester and avoided too close to delivery. Ideally, fetal maturity should be established prior to delivery. In general, radiation should be avoided during pregnancy with some exceptions. The placenta should be sent to pathology for all patients with malignancies diagnosed during pregnancy. Long-term follow-up of offspring exposed to chemotherapy is needed, especially regarding secondary malignancies and fertility.

The standard doses of drugs are recommended in pregnancy, but studies are lacking. Drug metabolism in pregnancy may warrant higher doses of some medications and lower doses of others. Prospective data is needed and, given the rarity of cancers in pregnancy, international collaboration is warranted.

Resources

In 1985, the National Cancer Institute established The Registry of Pregnancies Exposed to Cancer Chemotherapy, which has since been moved to the University of Pittsburgh Genetics Institute (Phone: +1-412-6414168). In 1985, Mother Risk in Toronto, Canada, started the Consortium of Cancer in Pregnancy Evidence (CCoPE) in an attempt to establish an international database (Phone: +1-416-8136780). A third registry exists at Robert Wood Johnson

Medical School in Camden, New Jersey (Phone: +1-856-7577876). Support for pregnant patients with cancer can be found at www.pregnantwithcancer.org.

Methods

A search in Pubmed/Medline was carried out from January 1, 1980, to December 31, 2008, looking for English-only articles using the formula "(pregnancy OR gestation) AND (leukemia OR lymphoma OR myeloma)" within titles and abstracts. A total of 896 articles were obtained, and after careful review of abstracts, 247 articles were deemed to be relevant for the present review. From the found articles, 117 focused on leukemia, 94 on lymphoma, 12 on myeloma, and 24 on other topics, such as MDSs and use of radiotherapy or chemotherapy during pregnancy in cancer patients.

A separate search was undertaken looking for abstracts presented at the American Societies of Hematology and Oncology (ASH and ASCO, respectively) Annual Meetings using a similar strategy. Fifty-two abstracts were obtained (43 abstracts from ASH and 9 from ASCO). Upon review, 10 ASH abstracts were considered relevant, while no ASCO abstracts were included in the present review.

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