Hematological malignancies during pregnancy (Review)

MERAV BARZILAI, IRIT AVIVI and ODELIA AMIT

Hematology and Hemato-Oncology Division, Tel Aviv Medical Center, Tel Aviv 6423906, Israel

Received September 6, 2017; Accepted June 26, 2018

DOI: 10.3892/mco.2018.1759

Abstract. Hematological malignancy during pregnancy is a rare event, therefore most data on this issue is based on case studies, retrospective studies and expert opinion. The purpose of the present narrative review was to provide an overview of the diagnosis and recommended management of the most common hematological malignancies during pregnancy, based on current literature, with clinical cases, and discussion of the diagnostic and therapeutic options. The therapeutic consensus while coping with hematological malignancies in pregnancy is to salvage the mother, while trying to preserve pregnancy and avoid treatment-related-toxicity to the fetus. In most scenarios, particularly during late trimesters, the goal is to administer the same treatment as outside of pregnancy, if possible. Further research is needed for better evidence-based management.

Contents

1. Introduction

The incidence of malignancy during pregnancy in the developed world is approximately 1/1,000. These neoplasms are mostly solid tumors, and their prevalence fits the general incidence of tumors during the reproductive age of women. The most common malignancies include; breast cancer, cervical cancer and melanoma. Hematological malignancies are less common, with lymphoma, mostly Hodgkin's lymphoma (HL) being the most frequent with an incidence of 1/6,000, due to its relative high occurrence in young adults (1).

Several hypotheses have been raised regarding a possible causative association between hematological malignancies and physiological changes occurring during pregnancy, for example; high levels of female sex hormones or the immunosuppressive effects occurring during pregnancy. To date, no such mechanisms have been proved regarding the development or the recurrence of hematological malignancies due to pregnancy (2). Due to the rarity of hematological malignancies during pregnancy, most of the literature is based on retrospective studies, expert opinion and case reports. In this review, we offer a general overview of the diagnosis and treatment of hematological malignancies occurring during pregnancy, by presenting hypothetical clinical cases and providing recommendations regarding management.

2. Clinical diagnosis and imaging

Early diagnosis evidently improves the outcome of most malignancies. Unfortunately, hematological malignancies occurring during pregnancy, especially non-Hodgkin's lymphoma (NHL), tend to be diagnosed relatively late, due to an overlap of signs and symptoms, characterizing both the malignancy and pregnancy (weakness, sweating, shortness of breath, abdominal/back pain). Furthermore, during pregnancy there is a tendency to avoid invasive and imaging diagnostic procedures, which may further delay the diagnosis.

Both lymph node biopsy and bone marrow biopsy, required for the diagnosis of lymphoma (HL/NHL) and leukemia respectively, are considered to be safe during pregnancy and should therefore not be delayed or avoided (3).

The main concern when using diagnostic imaging in pregnancy is fetal exposure to ionizing radiation. The fetus is most sensitive to radiation effects during organogenesis, particularly during the window of neural development between 8-15 weeks. Exposure to radiation may result in prenatal death, intrauterine growth retardation (IUGR), organ malformation, neurological sequela including small head size, mental retardation, and also an increased risk of childhood cancer. The specific risk depends on the gestational stage at the time of exposure and the radiation dose given. The accepted cumulative fetal exposure is generally up to 100 mGY (4). The radiation exposure associated with chest computed tomography (CT) is less than 100 mGY, therefore acceptable, especially in later gestational stages. Abdominal and pelvic CT scans, however, are prohibited,

Correspondence to: Professor Irit Avivi, Hematology and Hemato-Oncology Division, Tel Aviv Medical Center, 6 Weitzman Street, Tel Aviv 6423906, Israel
E-mail: iritavi@tlvmc.gov.il

Key words: hemotherapy during pregnancy, hematological malignancies, imaging during pregnancy, malignancy during pregnancy

as is Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) which is currently the gold standard for staging of most lymphomas outside pregnancy, providing simultaneously an anatomical and functional imaging of the involved sites (5-7). Ultrasound (US), though less sensitive than abdominal CT/PET-CT, remains a good alternative imaging, being both safe and available. Recently, magnetic resonance imaging (MRI) without contrast gadolinium is becoming an important imaging alternative. In contrast to US, which is more subjective and may be adversely affected by fetal position, oligohydramnios, or obesity, MRI's accuracy is not affected by these factors and thus increases its accuracy. Questions have been raised regarding potential teratogenecity and acoustic damage of this modality, however there is no supporting evidence in the literature and therefore MRI has become the preferable imaging modality during pregnancy (8,9).

3. General principles of therapy

The treatment of each malignancy is specific and optimally should not differ from the treatment given to non-pregnant women. However, because of the teratogenic effects of many most chemotherapeutic agents, treatment in the first trimester is generally contra-indicated. Therefore, when diagnosed in early gestational stage, women with aggressive disease, are recommended to undergo an elective termination of pregnancy followed by a prompt administration of therapy.

Chemotherapy. Physiological changes during pregnancy (increase in plasma volume, renal clearance and hepatic oxidation, third spacing and altered protein binding) affect the distribution, metabolism and excretion of chemotherapeutic drugs resulting in decrease in serum drug levels (10,11).

Chemotherapy dosage, should not be reduced, but calculated according to the current pregnancy body surface area (BSA) (11,12). Most chemotherapeutic agents cross the placenta, therefore exposure to chemotherapy at the time of organogenesis is associated with major malformations, spontaneous abortions and fetal death (13).

Exposure to chemotherapy in the implantation phase (first 14 days after conception) may result in miscarriage ('all or none' phenomenon miscarriage vs. normal embryo) while later, in the embryogenesis phase (day 14; week 8 after conception) it may result in teratogenic effects and major congenital anomalies (14,15). After the 1st trimester, the rate of fetal anomalies is lower and less predictable, but there is still a risk of organ damage [especially eyes, genitals, hematopoietic system and central nervous system (CNS)], intra uterine growth restriction (IUGR), intra uterine death, and preterm delivery (16). Potential teratogenic effects of different anti cancerous drugs (listed by organ involvement) and recommendations for use during pregnancy are presented in Table I (13-18).

Radiotherapy. Treatment of hematological malignancies is mainly based on systemic chemotherapeutic regimens. However, there are few clinical scenarios in which radiotherapy is considered, including stage I (localized), indolent lymphoma (e.g., follicular lymphoma), consolidation of bulky lymphadenopathy in patient with aggressive lymphoma [e.g., diffuse large B-cell lymphoma (DLBCL)] and in combination with short course chemotherapy in patients with early HL. Moreover, it may also has an important role in the treating hemato-oncological emergencies such as lymphoma that causes a spinal cord compression or superior vena cava syndrome (4). As previously mentioned, fetal exposure to radiation may result in malformations, IUGR and death. Moreover, it may potentially induce long-term sequelae such as cataract, cognitive impairment and the development of childhood cancer and is therefore generally not recommended during pregnancy (6,7). Nevertheless, in several clinical circumstances, where the radiation target is distant from the fetus (for example a cervical lymph node), radiotherapy may be considered. Consultation with a medical physicist is imperative, taking into account the expected cumulative radiation dosage, consideration of leaks, expected scatter of radiation and the use of abdominal shielding.

Maternal supportive care during therapy. Chemotherapy may result in neutropenia and increased risk for life threatening infections, requiring the administration of broad spectrum antibiotics and intensive support. Due to their potential teratogenicity, several antibiotics-including tetracyclines, aminoglycosides and trimethoprim (classified C and D according to FDA labeling categories) are relatively contraindicated during pregnancy (and during organogenesis in particular) (19). Blood products can be given safely as needed. The use of granulocyte-colony stimulating factor (G-CSF) during pregnancy is considered to be safe, although data are limited (20). Prospective studies provide reassuring information about the use of Odansteron and Promethazine as antiemetics during pregnancy (21). When anticoagulation is indicated, low molecular weight heparin (LMWH) is safe during pregnancy while warfarin is contraindicated due to its teratogenic effect (22).

Timing of delivery. Premature birth is an independent risk factor for neuro-developmental disorders, pulmonary dysfunction and ophthalmic disorders (23). Therefore, the goal is to continue the pregnancy up to at least week 35 (administrating the required chemotherapy during pregnancy) and avoid an iatrogenic early delivery. Of note, delivery should be planned at least 3 weeks after chemotherapy administration in order to avoid maternal and fetal myelosuppression. If an early delivery (<34 weeks) is required (due to fetal or maternal-related compilations), then, antenatal steroids should be given to minimize fetal-lung injury (14). Table II summarizes treatment strategies for several hematological malignancies, inside and outside of pregnancy.

4. Clinical cases

Case 1: Hodgkin's lymphoma. A 26-year-old patient, in her 10th week of pregnancy came with cervical lymphadenopathy, fever and sweating. An excisional biopsy revealed classical HL. X-ray showed a mediastinal mass. Total body MRI showed enlarged cervical and axillary nodes and a 5 cm mediastinal mass, with no evidence of infra-diaphragmatic involvement. She was diagnosed as stage II B HL. In the current case we will discuss the safety of anti-HL therapy during pregnancy,

Table I. Potential fetal toxicity caused by most common agents employed for treating lymphoma and leukemia.

		1st trimester			2nd and 3rd trimester		
Drug	Protocol	CNS/eye	Limb/skeleton	Cardiac	IUGR	LBW	Cytopenia
Cyclophosphamide	CHOP (NHL)	+	+	-	+	+	-
Doxorubicin/daunorubicin	HL (ABVD) NHL (CHOP) ALL (Induction) AML (Dauno-Cytarabine)	-	+	-	+	-	+
Cytarabine	AML (7+3) ALL (Induction)	-	+	-	+	+	+
Vincristine	NHL (CHOP)	-	+	+	±	±	±
Bleomycin	HL (ABVD)	-	-	-	-	-	+
ATRA	APL (Idarubicin +/- ATO)	+	-	+	±	±	±
Rithuximab (anti CD20)	NHL (R-CHOP)	-	-	-	+	-	+

CNS, central nervous system; IUGR, intra uterine growth restriction; LBW, low birth weight; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, rithuximab CHOP; ABVD, adriamycin, bleomycin, vincristine, doxorubicin.

especially during the first trimester. HL is the most common hematological malignancy reported during pregnancy, (most probably due to the higher incidence of this particular hematological malignancy in the relevant age group). As previously mentioned, the overlap between pregnancy related symptoms and B symptoms may lead to a delay in diagnosis. The most common chemotherapy regimen used for HL outside pregnancy is the ABVD (adriamycin. dacarbazine, bleomycin, vincristine and doxorubicin) regimen administered successfully with a high complete remission rate in most cases (24). ABVD is considered to be relatively safe beyond 1st trimester of pregnancy, whereas patients diagnosed in late 1st trimester are often considered for a short course of steroids or vinblastine as bridge therapy until second trimester (12). Short-term follow-up of newborns exposed to ABVD in utero, showed no increased risk for congenital abnormalities, though lower birth weight and prematurity were more common (14). Long term evaluation revealed no increased risk for cardiac toxicity (25). EscBEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine) a popular choice for patients diagnosed with advanced HL outside pregnancy (26) is not recommended during pregnancy due to its potential teratogenic effect, though data regarding its use during pregnancy are limited (2). In general, women diagnosed with HL during pregnancy have a favorable prognosis, with a similar long-term survival to matched non-pregnant patients and fetal outcome is also encouraging (27).

After discussing all therapeutic options, vinblastine monotherapy was chosen and administered till second trimester, followed by 5 cycles of ABVD regimen. She gave birth to a healthy baby and after delivery she was treated with involved field radiotherapy to a cervical node. PET-CT at the end of treatment showed complete response.

Case 2: Aggressive NHL. A 35-year-old woman during her 20th week of pregnancy presented with constitutional symptoms and enlarged cervical and supraclavicular lymph nodes. A lymph node biopsy showed DLBCL. Total body MRI showed lymphadenopathy on both sides of the diaphragm. Blood tests revealed anemia and elevated LDH. The bone marrow biopsy showed an extensive infiltration of large lymphoma cells. The patient was diagnosed with stage IV DLBCL.

The current case deals with the safety of anti-lymphoma therapy during second trimester pregnancy, the safety of rituximab (R) and type/timing of CNS prophylaxis (MTX). DLBCL is an aggressive lymphoma, therefore treatment should be started shortly after diagnosis, unless the patient has been diagnosed during the last weeks of pregnancy, or at the end of first trimester, where therapy may be delayed for 1-2 weeks if the clinical situation allows. When the diagnosis is made during second or third trimester, combination chemotherapy composed of R-CHOP can be safely administered (2). R is a monoclonal antibody directed against CD20, primarily expressed by mature B-cells. It has the ability for transplacental passage. A large retrospective study summarized the outcomes of offspring exposed to R in utero, and reported a slightly higher rate of preterm delivery and miscarriage (mostly when exposed during the first trimester, and when chemotherapy was co-administered. The rate of congenital malformations however, was not increased compared with that reported in the general obstetric population (28). Other potential uncommon outcomes were the development of transient cytopenia or B-cell depletion at birth, nevertheless, there was no significant increase in risk of infections (29). In summary, administration of the R-CHOP regimen during second and third trimester is considered to be relatively safe (2).

In some patients, defined to be at high risk for CNS relapse (bone marrow, orbit/nasopharynx/kidney or testis involvement/elevated LDH, high IPI score), there is also a need for intrathecal or intravenous administration of methotrexate (MTX) (17). As mentioned earlier, MTX is highly teratogenic, therefore it is generally contra-indicated during pregnancy.

Table II. Our recommendations to treatment of lymphoma and leukemia during pregnancy vs. conventional treatment outside pregnancy.

Malignancy	Treatment in pregnancy	Treatment outside of pregnancy
HL	1st trimester: Vinblastine till 2nd trimester, or observation until 2th trimester if asymptomatic and disease burden is low) 2nd or 3rd trimester: ABVD, (without dose reduction)	Chemotherapy (ABVD/BEACOPP +/- radiation)
NHL		
Indolent lymphoma	1st trimester→WW 2nd 3rd trimester→treat if symptomatic/progression: Local RT, chemotherapy- R-CHOP/RCVP	-Asymptomatic: WW-Symptomatic: Local: Irradiation Advanced: -Low burden: WW -high burden: R-CHOP
Aggressive lymphoma	1st trimester: If diagnosed early, PT is needed. If diagnosed at the end of first trimester, postpone therapy to 2nd (employing steroids as a bridge). 2nd or 3rd trimester: Treat as non-pregnant (R-CHOP) without CNS prophylaxis (if needed) until 3rd trimester	Chemotherapy (R-CHOP) +/- CNS prophylaxis (MTX)
Acute leukemia	1st trimester-PT ≥2nd trimester-induction regimen (cytarabine + daunorubicin)	Induction regimen (cytarabine + daunorubicin)

HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; PT, pregnancy termination; R-CHOP, rithuximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCVP, rithuximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ABVD, dacarbazine, bleomycin, vincristine, doxorubicin; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MTX, methotrexate; RT, radiotherapy; WW, watchful waiting.

Few studies that reviewed the outcome of MTX exposure during 2nd and 3rd trimester, reported an increased risk for fetal myelosuppression, but with no increased incidence of teratogenic events. Therefore, at present, MTX should be avoided, or at least withhold beyond week 20 of pregnancy (17,30,31).

The patient chose to continue pregnancy. She was treated with 6 cycles of R-CHOP and gave birth to a healthy baby in the 37th week. After delivery she was treated with 2 cycles of high dose MTX for CNS prophylaxis. PET-CT after completion of therapy showed complete remission.

Case 3: Acute myeloid leukemia (AML). A 37-year-old in her 21st week of her second pregnancy was referred to the ER due to shortness of breath, without chest pain, cough or fever. Physical examination revealed-saturations of 90% in room air, tachypnea 40/min, clear lungs and mild petechial rash on both legs. Complete blood count: 200,000 leukocytes, hemoglobin=8.2 gr/dl, platelets=70K. Chest X-ray showed diffuse infiltrates. Peripheral blood smear showed infiltration with blast cells. bone marrow aspiration and biopsy confirmed the diagnosis of AML.

This section deals with the therapeutic approach towards treating AML during pregnancy in terms of chemotherapy administration and its potential toxicity to the mother and fetus.

AML is an aggressive hematological malignancy characterized by highly rapid proliferation of clonal myeloid precursors with a reduced ability to differentiate into mature cells. As a result, bone marrow is substituted by leukemic cells called 'blasts', resulting in a reduction of normal blood cells (32). The patient in our case presented with shortness of breath, most probably secondary to leukostasis (the accumulation of blast cells in small lung blood vessels), though lung infection, pulmonary embolism and congestive heart failure, should be ruled out. Leukostasis may cause retinal and lung vessel occlusion, resulting in visual disturbance and dyspnea respectively. During pregnancy, this may result in placental vessel occlusion, leading to abnormal fetal development (33). In pregnant patients, similar to non-pregnant patients who present with symptomatic leukostasis, we promptly perform leukopheresis, to lower the white blood cell counts and prevent blood vessel occlusion (34). In a non-pregnant woman, the

management of a newly diagnosed AML would be prompt administration of induction therapy, aiming to achieve complete remission. Post induction therapy (in case CR is achieved), would include consolidation chemotherapy for favorable disease and allogeneic stem cell transplantation for patients with standard and unfavorable disease (2).

The standard induction chemotherapy for AML is the '7+3' regimen, which includes continuous infusion of high dose Cytarabine for 7 days in combination with anthracycline infusion during the first 3 days. Both agents are teratogenic (Table I) if given during organogenesis (Table I) (13,14,16,18). Hence, for pregnant women diagnosed during the first trimester, the common practice is early termination of pregnancy and prompt administration of induction therapy. For patients diagnosed during second trimester, pregnancy can be continued and induction therapy administered (35). Nevertheless, exposure to chemotherapy during the 2nd and 3rd trimester is still associated with an increased incidence of spontaneous abortions, preterm deliveries, IUGR and stillbirths. Notably, part of the inferior fetal outcome may be due to the consequences of leukemia significant anemia, neutropenia, thrombocytopenia and not only to treatment itself (34,36). Anthracyclines (Idarubicin, Daunorubicin, Epirubicin) are presumed to be more fetotoxic than Cytarabine. Idarubicin is the most lipophilic anthracycline and thus most toxic, due to its increased ability to cross the placenta. Therefore, the preferred anthracyclines used during pregnancy are Daunorubicin and Doxorubicin. Fetal exposure to anthracyclines has a relatively low risk of fetal abnormalities (malformations, death, spontaneous abortions and immaturity) when given after first trimester and long term follow-up studies failed to demonstrate cardiac toxicity (14,15,18).

Being diagnosed during 2nd trimester, pregnancy termination was elected. Cytogenetic profile was unfavorable and the patient was referred for an allogeneic transplantation.

Case 4: Chronic myeloid leukemia (CML). A 40-year-old woman, was in her 10th week of her second pregnancy when referred to the ER because of abnormal routine blood test results. She was not complaining of any symptoms. On complete blood count: hemoglobin=11.2 gr/dl, platelets=300K, WBC=30,000 with left shift and basophilia, 1% blasts. Bone marrow aspiration showed a similar picture, 1-2% blasts were counted. Test for BCR-ABL gene was positive and the patient was diagnosed with CML.

This section deals with the therapeutic options of treating CML in pregnancy. CML is a relatively slow growing myeloproliferative disease characterized by the excess production of mature and maturing granulocytes with normal differentiation. The median age is 50 years old, therefore it is uncommon in pregnancy. CML is uniquely associated with the (9:22) translocation which is a diagnostic hallmark. The BCR-ABL fusion oncogene encodes a constitutively active tyrosine kinase (37).

CML is often diagnosed in its chronic phase during routine blood tests, performed in asymptomatic subjects. Occasionally patients may complain of weakness and abdominal pain due to splenomegaly. The diagnosis of CML during pregnancy does not necessarily lead to the initiation of treatment. In patients presenting with markedly increased WBC resulting in a leukostasis picture, leukopheresis should be performed (38).

The initial choice for treating CML in non-pregnant patients is a tyrosine kinase inhibitor (TKI) (39). TKI's have revolutionized the course of CML, leading to clinical and molecular remissions, and providing long-term control in a majority of patients (40). The TKIs target the constitutively active TK which drives the pathological disease process and lower the levels of BCR-ABL fusion protein. The goal of TKI therapy in the era of imatinib, the first generation TKI, was to achieve a major molecular remission (MMR), defined as BCR-ABL/ABL levels <0.1% according to the international scale (IS). The introduction of second generation TKIs (nilotinib, dasatinib, bosutinib), which are more selective and potent, led to the definition of a new therapeutic cutoff, BCR-ABL ratio <0.01% IS, defined as deep molecular remission (MR_4) (41).

In addition to BCR-ABL, TKIs also inhibit other oncogenes, including PDGRF-α (platelet derived growth factor alpha), which are essential for embryonic implantation, gonadal development and fetal maturation and are therefore associated with fetal abnormalities (42). Several case reports and studies regarding the outcomes of imatinib. Therapy (the first generation TKI) during pregnancy were conducted, mostly in CML patients exposed to imatinib before and during the first trimester, until pregnancy was confirmed. Though most pregnancies had a normal outcome, there was still an increased risk for fetal abnormalities, including complex malformations (skeletal, renal, respiratory and gastro-intestinal), and spontaneous abortions, especially when the exposure was during organogenesis (43-45). Data regarding the teratogenicity of second generation TKIs also point towards significant fetal toxicity, a higher rate of abortions and abnormal pregnancies. Nilotinib may be safer than other TKIs, due to a lower placental transfer (46-48). However, contraception is recommended for CML patients on TKI therapy (49,50). Several trials have shown that the cessation of TKI in patients who attained a deep, long lasting molecular remission might be safe and feasible with 40% of patients remaining disease free for 24 months (51-53). TKIs may be stopped in CML patients who plan to become pregnant, if they meet stringent criteria for TKI discontinuation, including at least 2 years documented MR_4 response with monitoring of BCR-ABL levels throughout pregnancy (54).

In the pre-TKI era, the combination therapy of interferon alpha (IFN-α) and hydroxyurea was used for clinical and molecular control of CML. However, hydroxyurea is embryotoxic according to animal models, with a high incidence of craniofacial and spinal defects; hence it is contraindicated during pregnancy (55). IFN-α is safe during pregnancy after organogenesis is completed, unfortunately, its efficacy is significantly inferior to TKIs, and it also associated with fever, chills and flu-like symptoms which can be hard to tolerate (56,57).

When CML is accompanied by extremely high platelet counts, there is an increased risk of thrombosis. This risk is even higher during pregnancy, considering that pregnancy itself is a hypercoagulable state. Therefore, when platelet counts are higher than $500x10^3/\mu l$ during pregnancy, treatment with aspirin is recommended (49). Anticoagulant therapy should also be initiated in patients with a personal history of thrombosis. Platelet pharesis is usually preserved for women who present with an

extremely high platelet count, accompanied by acute thrombosis or massive bleeding due to acquired Von Willebrand disease (58).

The patient was frequently followed during pregnancy. WBC counts stayed below 50K and she remained asymptomatic. Therefore, no therapy was initiated. She gave birth to a healthy baby and after the labor started TKI therapy.

5. Summary

Fortunately, hematological malignancies during pregnancy are not a common finding. Yet, their diagnosis frequently leads to complex ethical and medical dilemmas that require a multidisciplinary approach. The therapeutic consensus is to salvage the mother, while trying to preserve pregnancy and avoid treatment-related-toxicity to the fetus. In most scenarios, especially during late trimesters, the aim is to administer the same treatment as outside of pregnancy. Further research is however needed for better evidence-based management.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MB wrote the manuscript. OA and IA helped in writing the manuscript. All authors read and approved of the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Pavlidis NA: Coexistence of pregnancy and malignancy. Oncologist 7: 279-287, 2002.
2. Lishner M, Avivi I, Apperley JF, Dierickx D, Evens AM, Fumagalli M, Nulman I, Oduncu FS, Peccatori FA, Robinson S, *et al:* Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. J Clin Oncol 34: 501-508, 2016.
3. Pereg D, Koren G and Lishner M: The treatment of Hodgkin's and non-Hodgkin's lymphoma in pregnancy. Haematologica 92: 1230-1237, 2007.
4. Fenig E, Mishaeli M, Kalish Y and Lishner M: Pregnancy and radiation. Cancer Treat Rev 27: 1-7, 2001.
5. Shaw P, Duncan A, Vouyouka A and Ozsvath K: Radiation exposure and pregnancy. J Vasc Surg 53 (1 Suppl): 28S-34S, 2011.
6. Chandra V, Dorsey C, Reed AB, Shaw P, Banghart D and Zhou W: Monitoring of fetal radiation exposure during pregnancy. J Vasc Surg 58: 710-714, 2013.
7. Groen RS, Bae JY and Lim KJ: Fear of the unknown: Ionizing radiation exposure during pregnancy. Am J Obstet Gynecol 206: 456-462, 2012.
8. Kawabata I, Takahashi Y, Iwagaki S and Tamaya T: MRI during pregnancy. J Perinat Med 31: 449-458, 2003.
9. Bulas D and Egloff A: Benefits and risks of MRI in pregnancy. Semin Perinatol 37: 301-304, 2013.
10. Anderson GD: Pregnancy-induced changes in pharmacokinetics: A mechanistic-based approach. Clin Pharmacokinet 44: 989-1008, 2005.
11. Feghali M, Venkataramanan R and Caritis S: Pharmacokinetics of drugs in pregnancy. Semin Perinatol 39: 512-519, 2015.
12. Autio K, Rassnick KM and Bedford-Guaus SJ: Chemotherapy during pregnancy: A review of the literature. Vet Comp Oncol 5: 61-75, 2007.
13. Van Calsteren K: Chemotherapy during pregnancy: Pharmacokinetics and impact on foetal neurological development. Facts Views Vis Obgyn 2: 278-286, 2010.
14. Abdel-Hady el S, Hemida RA, Gamal A, El-Zafarany M, Toson E and El-Bayoumi MA: Cancer during pregnancy: Perinatal outcome after in utero exposure to chemotherapy. Arch Gynecol Obstet 286: 283-286, 2012.
15. Vandenbroucke T and Amant F: Development of children born to mothers with cancer during pregnancy: Comparing in utero chemotherapy-exposed children with nonexposed controls. Am J Obstet Gynecol 212: 830-831, 2015.
16. Cardonick E and Iacobucci A: Use of chemotherapy during human pregnancy. Lancet Oncol 5: 283-291, 2004.
17. Abramson JS, Hellmann M, Barnes JA, Hammerman P, Toomey C, Takvorian T, Muzikansky A and Hochberg EP: Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 116: 4283-4290, 2010.
18. Germann N, Goffinet F and Goldwasser F: Anthracyclines during pregnancy: Embryo-fetal outcome in 160 patients. Ann Oncol 15: 146-150, 2004.
19. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS and McLaughlin M: A review of antibiotic use in pregnancy. Pharmacotherapy 35: 1052-1062, 2015.
20. Boxer LA, Bolyard AA, Kelley ML, Marrero TM, Phan L, Bond JM, Newburger PE and Dale DC: Use of granulocyte colony-stimulating factor during pregnancy in women with chronic neutropenia. Obstet Gynecol 125: 197-203, 2015.
21. Larrimer MB, Dajani NK, Siegel ER, Eswaran H, Newport DJ and Stowe ZN: Antiemetic medications in pregnancy: A prospective investigation of obstetric and neurobehavioral outcomes. Am J Obstet Gynecol 210: e1-e7, 2014.
22. Goland S and Elkayam U: Anticoagulation in pregnancy. Cardiol Clin 30: 395-405, 2012.
23. Gibbs RS, Romero R, Hillier SL, Eschenbach DA and Sweet RL: A review of premature birth and subclinical infection. Am J Obstet Gynecol 166: 1515-1528, 1992.
24. Boleti E and Mead GM: ABVD for Hodgkin's lymphoma: Full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 18: 376-380, 2007.
25. Avilés A, Neri N and Nambo MJ: Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. Ann Oncol 17: 286-288, 2006.
26. Ansell SM: Hodgkin lymphoma: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 89: 771-779, 2014.
27. Weibull CE, Eloranta S, Smedby KE, Björkholm M, Kristinsson SY, Johansson AL, Dickman PW and Glimelius I: Pregnancy and the risk of relapse in patients diagnosed with Hodgkin lymphoma. J Clin Oncol 34: 337-344, 2016.
28. Chakravarty EF, Murray ER, Kelman A and Farmer P: Pregnancy outcomes after maternal exposure to rituximab. Blood 117: 1499-1506, 2011.
29. Klink DT, van Elburg RM, Schreurs MW and van Well GT: Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. Clin Dev Immunol 2008: 271363, 2008.
30. Hyoun SC, Običan SG and Scialli AR: Teratogen update: Methotrexate. Birth Defects Res A Clin Mol Teratol 94: 187-207, 2012.

31. Lloyd M, McElhatton P, Carr M, Hall G and Hughes R: Methotrexate in pregnancy. Rheumatology (Oxford) 44: 697, 2005.
32. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, *et al*: Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129: 424-447, 2017.
33. Ganzel C, Becker J, Mintz PD, Lazarus HM and Rowe JM: Hyperleukocytosis, leukostasis and leukapheresis: Practice management. Blood Rev 26: 117-122, 2012.
34. Chang A and Patel S: Treatment of acute myeloid leukemia during pregnancy. Ann Pharmacother 49: 48-68, 2015.
35. McGregor AK and Das-Gupta E: Acute myeloid leukaemia in pregnancy. Br J Haematol 170: 441-442, 2015.
36. Milojkovic D and Apperley JF: How I treat leukemia during pregnancy. Blood 123: 974-984, 2014.
37. Maru Y: Molecular biology of chronic myeloid leukemia. Cancer Sci 103: 1601-1610, 2012.
38. Bazarbashi MS, Smith MR, Karanes C, Zielinski I and Bishop CR: Successful management of Ph chromosome chronic myelogenous leukemia with leukapheresis during pregnancy. Am J Hematol 38: 235-237, 1991.
39. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, *et al*: European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122: 872-884, 2013.
40. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, Baccarani M, Deininger MW, Cervantes F, Fujihara S, *et al*: Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 376: 917-927, 2017.
41. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, Kim DW, Kim TD, Khoury HJ, Le Coutre P, *et al*: European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 30: 1648-1671, 2016.
42. Nurmio M, Kallio J, Toppari J and Jahnukainen K: Adult reproductive functions after early postnatal inhibition by imatinib of the two receptor tyrosine kinases, c-kit and PDGFR, in the rat testis. Reprod Toxicol 25: 442-446, 2008.
43. Apperley J: Issues of imatinib and pregnancy outcome. J Natl Compr Canc Netw 7: 1050-1058, 2009.
44. Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, Koller C, Giles F, Keating M, Talpaz M and Cortes J: Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 24: 1204-1208, 2006.
45. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G and Apperley JF: The effects of imatinib on pregnancy outcome. Blood 111: 5505-5508, 2008.
46. Barkoulas T and Hall PD: Experience with dasatinib and nilotinib use in pregnancy. J Oncol Pharm Pract 24: 121-128, 2018.
47. Cortes JE, Abruzzese E, Chelysheva E, Guha M, Wallis N and Apperley JF: The impact of dasatinib on pregnancy outcomes. Am J Hematol 90: 1111-1115, 2015.
48. Hermel DJ, Chiu V, Hermel MH, Tulpule A and Akhtari M: Cardiac birth defects in a twin infant born to a woman with chronic myeloid leukemia on dasatinib. J Oncol Pharm Pract: Jan 1, 2017 (Epub ahead of print).
49. Abruzzese E, Trawinska MM, de Fabritiis P and Baccarani M: Management of pregnant chronic myeloid leukemia patients. Expert Rev Hematol 9: 781-791, 2016.
50. Law AD, Dong Hwan Kim D and Lipton JH: Pregnancy: Part of life in chronic myelogenous leukemia. Leuk Lymphoma 58: 280-287, 2017.
51. Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, Guerci-Bresler A, Legros L, Varet B, Gardembas M, *et al*: Long-term follow-up of the French Stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol 35: 298-305, 2017.
52. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, Hellmann A, Stentoft J, Conneally E, García-Gutiérrez V, *et al*: Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: Results from the ENESTfreedom study. Leukemia 31: 1525-1531, 2017.
53. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, Dang P, Goyne JM, Slader C, Filshie RJ, *et al*: Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: Results from the TWISTER study. Blood 122: 515-522, 2013.
54. Pallera A, Altman JK, Berman E, Abboud CN, Bhatnagar B, Curtin P, DeAngelo DJ, Gotlib J, Hagelstrom RT, Hobbs G, *et al*: NCCN guidelines insights: Chronic myeloid leukemia, version 1.2017. J Natl Compr Canc Netw 14: 1505-1512, 2016.
55. Celiloglu M, Altunyurt S and Undar B: Hydroxyurea treatment for chronic myeloid leukemia during pregnancy. Acta Obstet Gynecol Scand 79: 803-804, 2000.
56. Fiorani C, Tonelli S, Casolari B and Sacchi S: The role of interferon-alpha in the treatment of myeloproliferative disorders. Curr Pharm Des 5: 987-1013, 1999.
57. Lipton JH, Derzko CM and Curtis J: Alpha-interferon and pregnancy in a patient with CML. Hematol Oncol 14: 119-122, 1996.
58. Wright CA and Tefferi A: A single institutional experience with 43 pregnancies in essential thrombocythemia. Eur J Haematol 66: 152-159, 2001.