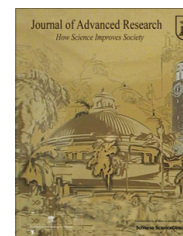




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REVIEW

Hematologic malignancies during pregnancy: A review

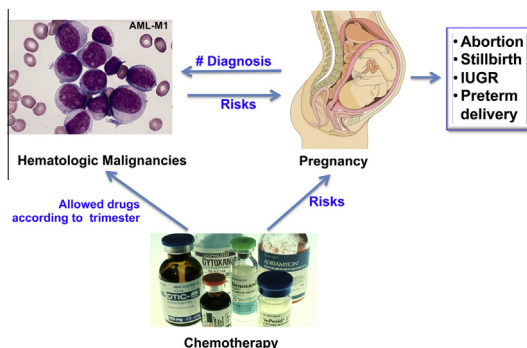


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GRAPHICAL ABSTRACT



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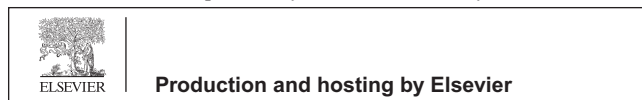
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ABSTRACT

Malignancy is the second most common cause of mortality in the reproductive period and it complicates up to one out of every 1000 pregnancies. When cancer is diagnosed during pregnancy, the management approach must take into consideration both the mother and her fetus. Hematologic cancers diagnosed in pregnancy are not common, resulting in paucity of randomized controlled trials. Diagnosis of such malignancies may be missed or delayed, as their symptoms are similar to those encountered during normal pregnancy. Also, many imaging studies may be hazardous during pregnancy. Management of these malignancies during pregnancy

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induces many treatment-related risks for mother and baby and should consider patient's preferences for pregnancy continuation. In this article, hematologic malignancies diagnosed in pregnant patients including acute leukemias, chronic myeloid leukemia, lymphomas, multiple myeloma and myeloproliferative neoplasms, will be reviewed, including diagnostic and management strategies and their impact on the pregnant patient and the developing fetus.

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Introduction

Having malignancy during pregnancy may put the patient and the treating physician in a very serious situation, as weighing the risk of cancer versus the lethal effect of the chemotherapy used for its treatment is a very tough issue. So it is very important to address whom, when, and how to treat those patients. That is to say treating physician should ask himself some questions. The first is would this type and/or stage of the disease needs immediate intervention or treatment could be postponed till delivery. The second question is how can he treat this case during pregnancy using the safest road to reach a safe place, meaning that which type of chemotherapy would the mother tolerate and exert no or little side effects on the fetus during different trimesters of pregnancy.

Incidence

Cancer is diagnosed in approximately one out of 1000 pregnant women and this incidence is expected to grow due to the rising median age at pregnancy. The most common cancers associated with pregnancy are cervical (1.2:10000 pregnancies), breast cancer (1:3000–10000), melanoma (2.6:1000), lymphomas (1:1000–6000) and leukemias (1:75000–100000). Hematologic malignancies, which are considered to be diseases of old age, such as multiple myeloma (MM) and myeloproliferative neoplasms (MPNs), are recently more commonly encountered while the patients are pregnant owing to the rising median age at pregnancy, improved diagnostic molecular

techniques used in MPNs and better overall survival (OS) in MM. On the other hand myelodysplastic syndrome (MDS), and chronic lymphocytic leukemia (CLL) generally occur at an older age, so they are rarely diagnosed during pregnancy [1].

Diagnosis and staging of cancer during pregnancy

Several procedures are considered safe to be performed during any stage of pregnancy such as core needle or excisional biopsies and bone marrow (BM) biopsy [2].

Computed tomography (CT) scans and positron emission tomography (PET) scans should not be performed for staging of lymphoma during pregnancy due to the risk of radiation exposure of the fetus [3]. Ultrasonography can be safely used during pregnancy, while plain chest X-ray (CXR) can be performed, if required, in pregnant women with adequate abdominal shielding. Magnetic resonance imaging (MRI) should be avoided in the first trimester of pregnancy, while it can be performed during second and third trimesters if it is strongly indicated assuming that its results would significantly influence the management plan [4]. Gadolinium (a contrast medium used in MRI) should not be used in the first trimester, as it crosses the placenta and causes fetal malformations [5]. Gadolinium MRI scans can be used during second and third trimesters if strongly indicated [1].

Isotopic bone scans are generally not recommended during pregnancy unless there are no other means of detecting bone metastases and results would alter the treatment strategy. On the other hand, MRI has a specificity of 91% for the detection of bone metastases in hematologic cancers [6].

Acute leukemias

Acute leukemia (AL) developing during pregnancy necessitates a multidisciplinary team management including a medical oncologist, an obstetrician, and a neonatologist. It requires immediate management irrespective of the gestational age as any delay in therapy can seriously affect the prognosis of the mother [7]. Recommendations for management of these patients are hampered by the rarity of these conditions in pregnancy and insufficiency of available data in the literature. The largest experience of AL in pregnancy came from Mayo Clinic (1962–1999), where 17 cases of AL in pregnancy were treated [8]. Another retrospective study of 37 AL patients from 13 French centers was performed (1988–2003), in which vincristine, doxorubicin, daunorubicin, idarubicin, cytarabine, cyclophosphamide, asparaginase, mercaptopurine, prednisone, methotrexate, mitoxantrone, and all-trans-retinoic acid (ATRA) have been utilized during all trimesters [9]. In a review of 152 patients with ALL and AML, six neonates with congenital abnormalities, 12 with intrauterine growth retardation (IUGR), 11 fetal deaths, and 2 neonatal deaths were recorded [10].

Acute myeloid leukemia (AML)

The majority of cases with AML are diagnosed in the second or third trimesters. The standard regimen for induction consists of cytarabine and an anthracycline [11].

Exposure to cytarabine in the first trimester can cause severe limb malformations and its use is not advocated and termination is strongly preferred. In the second and third trimesters, it was associated with transient cytopenias, intrauterine fetal death, IUGR, and neonatal death from sepsis and gastroenteritis [10].

Daunorubicin is the anthracycline of choice in pregnancy. Although rare cases of fetal cardiotoxicity have been documented with anthracycline use, fetal cardiac function should be monitored during pregnancy [12].

For relapsed AML, termination of pregnancy is highly recommended, because treatment usually requires high-dose chemotherapy, and BM transplantation, which cannot be given safely in pregnancy [13].

In summary, counseling and termination of pregnancy in first trimester are recommended. In second and third trimesters, induction chemotherapy with daunorubicin and cytarabine can be introduced, with regular surveillance for the development of congenital abnormalities and monitoring of fetal cardiac function.

Acute promyelocytic leukemia (APL)

The hematologic manifestations of APL, such as pancytopenia, disseminated intravascular coagulation and hyperfibrinolysis represent a medical emergency during pregnancy. Women with APL diagnosed during pregnancy have higher risks of abortion, perinatal mortality, IUGR, and preterm delivery [9]. Clinical sequelae include increased bleeding, infection, inflammation, placental abruption, and decreased oxygen and nutrient delivery [14].

APL is usually treated by ATRA combined with anthracycline-based chemotherapy (idarubicin or daunorubicin). It has a complete remission rate of >90% and a potential cure in up to 80%. During pregnancy, this drug regimen is controversial due to the potential teratogenic effects and medication-related complications such as fatal retinoic acid syndrome [15]. Retinoic acid in low doses is especially harmful to the fetus during weeks 3–5 of gestation. Complications that can result include craniofacial alterations, neural tube defects, cardiovascular malformations, and thymic aplasia [16]. However, the risk of teratogenic effects during the second and third trimesters of pregnancy is low [17].

In the first trimester, ATRA should be avoided, and women should be counseled to consider termination. Should termination of the pregnancy be unacceptable, treatment with an anthracycline should be started and ATRA introduced in the second trimester. Daunorubicin is the anthracycline of choice, not only because there is more experience of its use in pregnancy, but also because it may induce less fetal toxicity than idarubicin. Treatment after the beginning of the second trimester results in a more successful outcome. Chemotherapy does not appear to cause congenital abnormalities, but undoubtedly increases the risk of abortion, prematurity, low birth weight, neonatal neutropenia, and sepsis. Potentially, ATRA could be given alone with the addition of the anthracycline after delivery. This has resulted in remission rates equivalent to combination of ATRA and chemotherapy. However, using ATRA as a single agent increases the risk of ATRA syndrome (APL differentiation syndrome) and possible ATRA resistance. Alternatively, use of ATRA and an anthracycline is rec-

ommended for high-risk patients with hyperleukocytosis. Arsenic trioxide (ATO), which has been used for relapsed APL patients and more recently explored as first-line therapy, cannot be recommended at any stage of pregnancy as it is highly embryotoxic [13,16,17].

Acute lymphoblastic leukemia (ALL)

In a review by Terek et al. [18], 28% of leukemia cases diagnosed during pregnancy are ALL. In this study, a total of 17 patients with ALL received chemotherapy between gestational age of 15 and 33 weeks. Most chemotherapy regimens included anthracyclines, vincristine and steroids. About half of the women in this study achieved remission while the other half either relapsed or died from progression of the disease. Some infants were born with transient pancytopenia, respiratory distress and preterm delivery [18].

Before week 20 of gestation, termination should be considered, and then conventional therapy instituted. After the 20th week, bridging chemotherapy without methotrexate until the third trimester can be instituted. A brief period of treatment with prednisolone alone for 1–2 weeks may allow the patient to enter the period of gestation post 20 weeks in order to then receive more intensive chemotherapy. A similar approach with prednisolone alone can also be recommended for patients presenting close to 32 weeks of pregnancy. Methotrexate, an important drug in the treatment of ALL, should be avoided in first and second trimesters of pregnancy and may be used, if necessary, with caution in the third trimester [13].

Chronic myeloid leukemia (CML)

Recent use of BCR–ABL1 tyrosine kinase inhibitors (TKIs) has led to marked improvement of survival in CML patients. Many young female CML patients may become pregnant during their lifetime. It is important to mention that TKIs can inhibit several proteins, which are important for gonadal development, implantation and fetal development, thus increasing the risk of toxicities to the embryo. Imatinib is shown to be embryotoxic in animals with varying effects on fertility. As pregnancy is rare in CML, there are no randomized trials to address the optimal management of this disease. However, there are several case reports on CML in pregnancy [19].

Imatinib, the first TKI approved for the treatment of CML, has revolutionized the results of therapy with complete cytogenetic remission and OS rates of 82% and 90% respectively. However, almost one-third of patients need to be switched to another line of therapy due to resistance and/or intolerance to imatinib [20]. Nilotinib, dasatinib, bosutinib and more recently ponatinib, are safe and efficient drugs for treatment of patients with chronic phase (CP) CML, who are imatinib intolerant or resistant [21–23].

As the lifespan of patients responding to different TKIs is prolonged, many women in reproductive period may seek medical advice for the possibility of further pregnancy. These women should be clearly informed about the risks of becoming pregnant while on therapy and the possibility of a loss of response after drug discontinuation to continue pregnancy. However, pregnancy can be planned with sustained optimal response to TKIs [24].

There is limited information about the use of second and third generation TKIs during pregnancy. Forty-five women have been reported of nilotinib exposure during pregnancy, with only one case of fetal abnormalities ending into pregnancy termination and another case of fetal death due to congenital transposition of great vessels [25]. Dasatinib should be used with much caution during pregnancy due to more potent and wider range of signaling pathway inhibition including platelet-derived growth factor receptor- α [26]. There are no available data regarding patients receiving bosutinib or ponatinib during pregnancy [25].

In a female patient in the childbearing period, effective contraception should be suggested at diagnosis. Conception should be only scheduled after achievement of a sustained major molecular response (MMR), or a deep molecular response (e.g. MR^{4.5}) for at least 2 years. TKIs should be discontinued just before conception. TKIs should not be used during the period of fetal organ formation (weeks 5–13 of pregnancy). Quantitative Polymerase chain reaction (Q-PCR) tests for BCR/ABL: ABL ratio must be monitored every 1–2 month to assure the sustainability of molecular response. In case of hematologic or cytogenetic relapse, restarting treatment can be considered. Interferon (IFN) can be used safely throughout gestation [27]. Hydroxyurea may be considered to treat leukocytosis after fetal organogenesis [28]. Imatinib and nilotinib have limited placental transfer and can be used, if strongly indicated, after formation of placenta [29]. In contrast, dasatinib can pass extensively through the placenta, and it should not be used all through the pregnancy [30].

After labor, TKI therapy can be delayed to permit breastfeeding, only in case of stable molecular response. If it is important to restart therapy with TKI, breast milk is recommended during the first few postpartum days to deliver the colostrum to the baby [25].

Hazards of use of TKIs in pregnancy

Only few case reports of CML patients treated with TKIs during pregnancy are published. Most of these patients were treated with imatinib. In a study of 180 females treated with imatinib during pregnancy was performed, 50% of the patients delivered normal infants, and 28% underwent elective terminations (11% of them following identification of abnormalities). Abnormalities were identified in 12 infants with 9 of those defects occurring in the infants with known first trimester exposure to imatinib. In conclusion, most pregnancies exposed to imatinib are likely to have a successful outcome; however, there remains a risk that exposure may result in serious fetal malformations [31].

Fewer cases of exposure to newer TKIs during pregnancy have been also reported. One case of exposure to nilotinib during the first trimester was described in a patient who unexpectedly became pregnant while taking nilotinib until 7.4 weeks of pregnancy. Her baby was delivered without any congenital anomaly [32]. The outcome of pregnancy in 46 CML patients who received dasatinib while pregnant was recently reported. Live births occurred in 20 (43%) patients including 15 healthy and 5 abnormal infants with IUGR and/or premature delivery. Termination of pregnancy occurred in 26 (57%) patients (8 spontaneous and 18 elective). Seven pregnancies resulted in fetal and infant complications including 2 cases of hydrops

fetalis, 2 cases of CNS abnormalities, and a case with renal tract abnormalities [33].

Lymphoma

Staging methods for lymphoma during pregnancy are limited only to CXR with protective shields for the abdomen, abdominopelvic US and BM biopsy. BM biopsy is recommended for patients with lymphoma especially those with systemic (B) symptoms, and/or peripheral blood cytopenias [34,35]. Laboratory workup should also include complete blood count, erythrocyte sedimentation rate, LDH, kidney function and liver function tests including serum alkaline phosphatase. However, the latter is highly elevated in the third trimester of pregnancy and may not be useful [36]. Abdominal disease can be also evaluated with non-contrast MRI [37,38]. In contrast, PET and gallium scans are not safe during pregnancy [39].

Non-Hodgkin lymphoma (NHL)

Pregnancy itself may produce symptoms similar to those of lymphoma leading to a significant delay in diagnosis of such patients and a higher frequency of advanced disease [40]. Also in pregnancy-associated NHL, there is a higher frequency of involvement of reproductive organs due to their increased blood flow and increased hormone receptor expression during pregnancy [41]. In a systematic review of pregnant women with NHL (no = 121), 91 (75%) patients had stage IV disease with involvement of reproductive organs (mostly the breast) seen in 49% of them [42].

Indolent lymphoma

Due to the nonaggressive nature of indolent lymphomas, their definitive therapy can be delayed until the second trimester of pregnancy, or even until delivery. Rituximab monotherapy can be given safely during the first trimester if there is an urgent need for treatment. R-CVP regimen (rituximab, cyclophosphamide, vincristine and prednisone) or R-CHOP regimen (R-CVP + doxorubicin) can be used during the second or third trimester, whereas fludarabine-based regimens are not recommended [42].

Bendamustine became the standard of care as frontline therapy in Western world. Bendamustine has been assigned to pregnancy category D by the US Food and Drug Administration (FDA). Animal studies have revealed skeletal and visceral malformations, decreased fetal body weights, a significant increase in external and internal malformations, as well as embryo and fetal lethality. There are no controlled data in human pregnancy. Bendamustine should only be given during pregnancy when there are no alternatives and benefit outweighs risk.

Aggressive lymphomas

Highly aggressive lymphomas (including diffuse large B-cell, mantle cell and mature T-cell lymphomas) diagnosed in pregnancy may be distinguished by an aggressive nature with worse prognosis due to delay in diagnosis, and insufficient therapy used. When adequate chemotherapy is given, prognosis of

pregnant patients with NHL is similar to that of non-pregnant patients [40].

In the majority of patients with aggressive NHL diagnosed, during pregnancy, early therapy with chemotherapy combination regimens (such as CHOP) is usually needed. In the first trimester, the safety of CHOP protocol is not guaranteed and termination of pregnancy is usually advocated [40,43]. In some NHL patients with stage I/II disease with lower tumor burden, who are diagnosed in the first trimester, careful follow-up till the second trimester followed by proper chemoimmunotherapy may be indicated.

R-CHOP can be given more safely during the second or third trimester [40,43,44]. In a multicenter study, ninety pregnant women with aggressive lymphoma received the standard chemoimmunotherapy regimens in the second or third trimester of pregnancy with low frequency of maternal and fetal problems [41].

Highly aggressive lymphomas

As in aggressive lymphomas, the fulminant course and rapid progression of highly aggressive lymphomas such as lymphoblastic and Burkitt's lymphomas necessitates prompt initiation of aggressive treatment. High-dose methotrexate, which is usually included in chemotherapeutic regimens for these lymphomas, is highly toxic to the embryo if used in first trimester. Thus, pregnancy termination is strongly advocated in such cases [45].

Although methotrexate use during the second and third trimesters may not be teratogenic, it is found to be associated with severe fetal myelosuppression [40].

Rituximab during pregnancy

Many case reports of rituximab use during pregnancy have been published, mainly for benign diseases and they did not show a higher risk of teratogenicity [46,47]. Use of rituximab for treatment of lymphoma in early pregnancy, may lead to a temporary fetal B-cells depletion, followed however with rapid recovery of B-cells [48].

Pregnancy outcomes were reported in a retrospective study of 153 pregnant patients exposed to rituximab. Live births were reported in ninety cases and the majority of them were not complicated. Neonatal complications included transient leucopenia with or without infections [49].

In conclusion, the beneficial value of rituximab therapy for aggressive lymphomas during the second or third trimester of gestation is greater than its hazards to the fetus. In the first trimester, rituximab use cannot be recommended, although the data on teratogenicity are limited.

Hodgkin lymphoma (HL)

ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine), the commonest chemotherapy regimen used for HL, should not be used during the first trimester, as information with respect to its safety is restricted. There are no available safety data regarding the use of other chemotherapeutic regimens used for treatment of HL such as "Stanford V" or "BEACOPP" during pregnancy.

Patients diagnosed with advanced HL at first trimester of gestation, should immediately receive chemotherapy with termination of pregnancy. Early-stage HL diagnosed in the first trimester could be closely observed for development of disease progression and begin chemotherapy in the second trimester. In some cases in first trimester, localized radiotherapy to cervical and/or axillary area with abdominal shielding is an option of therapy of HL [34,38,40,50].

Most pregnant women diagnosed with HL during the second and third trimesters can be managed with ABVD. In some cases diagnosed with localized stage (IA or IIA) disease in the late second or third trimester, chemotherapy can be postponed until after delivery allowing complete staging and selection of the proper therapy after labor. However, there are no randomized controlled trials comparing the results of early versus deferred therapy in such patients [38].

The 20-year survival rate of pregnant women with HL was similar to that of matched non-pregnant women with HL. In addition, the incidence of preterm delivery or IUGR was not higher in pregnant women with HL [51].

Multiple Myeloma (MM)

Pregnant patients diagnosed with symptomatic MM need prompt therapy. Immunomodulatory drugs such as thalidomide and lenalidomide may induce marked teratogenicity, and should be avoided during the whole pregnancy period [52]. Also, bortezomib cannot be recommended in pregnant patients, as there are few data about its safety.

Corticosteroids are the safest therapy of MM during pregnancy, and can be used as a monotherapy in patients with mildly symptomatic disease until delivery. In rapidly progressive disease, an intensive combination therapy is usually required. If this progressive disease is diagnosed in the first trimester, termination of pregnancy is recommended. If the patient has an extensive pelvic or vertebral bone disease, Cesarean section is preferred to avoid trauma resulting from vaginal delivery [14].

Ph-negative myeloproliferative neoplasms (MPNs)

Only limited data are available about polycythemia vera (PV) and essential thrombocythemia (ET) developing during pregnancy [53]. In these patients, there is an increased incidence of abortion (twice as normal), IUGR, and intrauterine death. Maternal complications occur in about 8% of patients [54,55].

Several factors may influence the therapeutic decision for PV/ET including disease-related and pregnancy-related features. High-risk pregnancy is defined by presence of any of the following factors: previous thrombosis/hemorrhage in the mother, previous pregnancy-related complications attributable to PV/ET, severe preeclampsia, abruptio placentae, and unexplained recurrent first trimester fetal loss, IUGR, intrauterine death [54]. The plasma volume starts to increase from the second trimester onward leading to reduction of hematocrit (Hct) and platelet count; then, these levels start to rise again after delivery leading to an increased thrombotic risk. Close monitoring by weekly blood counts is important during the first six weeks postpartum to detect rebound thrombocytosis or polycythemia [55].

In PV, it is recommended to maintain the Hct within the normal range of the contemporary trimester of pregnancy. In ET, low dose aspirin is safe and beneficial during pregnancy. In the absence of obvious contraindications, all PV and ET patients should receive aspirin 75 mg daily throughout gestation. From the day of delivery, aspirin is replaced by low molecular weight heparin (LMWH), for 6 weeks [55].

In high-risk pregnancy, LMWH is recommended throughout pregnancy and 6 weeks after labor. Cyto-reductive therapy is indicated when the platelet level rises above $>1000\text{--}1500 \times 10^9/l$ or when cardiovascular risk factors are present. Hydroxyurea and anagrelide should be avoided due to their teratogenic effects. The drug of choice is non-pegylated IFN, as it has no teratogenic effects in animals or adverse effects in the small numbers of patients who receive this drug during pregnancy. Pegylated forms of IFN (PEG-IFN) are potentially less safe during pregnancy, as animal studies showed an adverse effect on the fetus while there are no adequate well-controlled studies in humans (pregnancy category C). So, PEG-IFN should be used only when benefit to the mother outweighs risk to their fetus. Breast-feeding is safe with LMWH, but contraindicated with all cyto-reductive agents including IFN [56].

Conclusions

The prognosis of most pregnant women with hematologic malignancies is similar to that of matched nonpregnant women. Treatment strategy should put into consideration the severity of malignancy, the teratogenicity of available effective drugs and the necessity to continue pregnancy. During the first trimester, if chemotherapy is necessary, termination of pregnancy is generally indicated. The outcome of patients who receive chemotherapy in the second or third trimester is usually good.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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