REVIEW ARTICLE

Managing cancer during pregnancy: what evidence do we have?

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KEY WORDS

cancer in pregnancy, chemotherapy, congenital anomalies, fetal complications, trastuzumab

ABSTRACT

The diagnosis of cancer during the course of pregnancy is a challenging clinical situation both for the patient and the treating physicians. Given its relative rarity, evidence remains scarce as it is practically impossible to perform large prospective clinical trials. Another critical issue is the potential conflict between maternal and fetal wellbeing: this could result in undertreating pregnant women for fear of fetal toxicity, or in offering therapy that could result in fetal morbidity and mortality. While there are some general guidelines that can be applied for all tumor types, each disease has specific features that should be considered. In this review, we will consider the available evidence for managing pregnant women with cancer to provide some guidance for physicians dealing with these patients.

Introduction The diagnosis of cancer during the course of pregnancy is a challenging clinical situation. It is estimated that 1 in every 1000 pregnancies is complicated with cancer.[1] The most common tumors diagnosed during pregnancy are breast and cervical cancer, followed by melanoma, leukemia, and lymphoma. Given its relative rarity, evidence remains scarce as conduction of large prospective clinical trials is practically impossible. Thus, current knowledge is derived from small phase-2 studies, retrospective analyses, and systematic reviews of literature. This is particularly risky because important clinical decisions are made in the absence of strong evidence. Such decisions could result in undertreating pregnant women for fear of fetal toxicity, or in offering therapy that could lead to fetal morbidity and mortality. Therapeutic abortion is sometimes needed; however, it cannot be widely adopted in all cases for social and sometimes religious reasons. In addition, there is no evidence that abortion improves the prognosis of these cases. Hence, there is an urgent need to adopt customized treatment strategies for these patients.[2] While there are general rules that could be applied across the different diseases (TABLE), each disease has specific features that should be considered on treating every patient.

We will try to throw light on the available evidence for managing pregnant women with cancer in an attempt to provide some guidance for physicians dealing with these patients.

Breast cancer Breast cancer is the most common tumor diagnosed during pregnancy with an estimated 10,000 cases diagnosed every year worldwide. Pregnant breast cancer patients are commonly diagnosed with advanced disease, which is mainly related to diagnostic delay.[3] Local interventions (surgery and radiotherapy) in addition to systemic therapy like chemotherapy, hormonal and targeted agents were all described in managing pregnant breast cancer patients.

Available evidence strongly suggests that surgery can be performed safely any time throughout the pregnancy course.[4] The decision to proceed for conservative breast surgery or mastectomy should be decided as per routine guidelines. Sentinel lymph node sampling has been discouraged by several international guidelines including the European Society for Medical Oncology, American Society of Clinical Oncology, and the National Comprehensive Cancer Network, despite the absence of evidence showing detrimental effects. This was for fear that the fetus could be exposed to the radiolabel tracer that could potentially result in fetal anomalies. However, an earlier

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TABLE General consideration in managing pregnant women diagnosed with cancer

surgery	Can be performed anytime during the course of pregnancy. Surgeries with high morbidity (e.g., gastrointestinal/lung) are discouraged because they could compromise the pregnancy course. If urgently needed, abortion should be considered.
radiotherapy	A general rule is to avoid radiotherapy during pregnancy as possible; however, it is possible to be considered for the cervical and mediastinal region with adequate uterine shielding. It should be only performed in centers with experience in managing patients diagnosed with cancer during pregnancy.
chemotherapy	Avoid during the first trimester because it is associated with high risk of congenital anomalies and spontaneous abortion. Fractionation of the dose on weekly bases allows easy pregnancy monitoring, easy interruption of chemotherapy if needed; also results in shorter nadir periods, which facilitates easy interruption of pregnancy if needed. This approach is highly recommended.
hormonal agents	Should be avoided all through the pregnancy course.
time of delivery	Avoid delivery in the nadir period; avoid delivery before week 35 to avoid prematurity-related complications.

dosimetry study followed by a recent prospective study on 12 pregnant breast cancer patients by the same group, showed no congenital anomalies and no evidence of axillary recurrence at a median follow-up of 32 months.[5,6] Thus, it could be considered in selected patients and in centers with high experience using this technique.

Several publications have addressed the feasibility and safety of chemotherapy during pregnancy. Anthracyclines are the most commonly used agents with an apparent safety demonstrated when administered starting the second trimester.[7-9] Only 2 prospectively treated series were described in the adjuvant (neo) setting.[10,11] The first involved 57 patients, who were treated with the FAC regimen (5-flourouracil, doxorubicin, and cyclophosphamide) with doxorubicin given as a continuous infusion for 96 hours.[10] The second was published later by our group and involved 20 patients who were treated with weekly epirubicin 35 mg/m^2.[11] Both regimens were well tolerated with no apparent increase in the risk of pregnancy complications or fetal congenital anomalies. Hence, both options remain valid for treating breast cancer patients diagnosed during pregnancy. From a feasibility perspective, the continuous infusion of doxorubicin is not widely adopted, and thus might not be convenient during pregnancy. A potential advantage of the latter regimen is that the weekly fractionation results in low peak plasma concentration of epirubicin leading to low maternal toxicity and low placental transfer of the drug.[12] In addition, weekly application allows close monitoring of the pregnancy, which reassures both the patient and the treating physician. It also results in shorter nadir periods and thus allows easy interruption of pregnancy if needed.[12] However, outside pregnancy, this regimen is not routinely used in the adjuvant setting, but it is important to note that treatment period during pregnancy does not comprise the whole adjuvant treatment period, and reverting to more standardized regimens can be done following delivery.[12] Also, the differences between different anthracycline-based regimens are at best modest in terms of the effect on overall survival and are mainly attributed to the dose of anthracycline, which is very well preserved with a weekly epirubicin dose of 35 mg/m^2.[12]

Very few data is available regarding the safety of other chemotherapeutic agents. The use of methotrexate is strongly discouraged because it is used for induction of abortion.[13] Taxanes have been described in literature in around 30 pregnant breast cancer patients.[14] There is no evidence that they increase the risk of pregnancy complication. Thus, they remain the second best option in case anthracyclines are contraindicated for any reason. Data on other agents are even scarcer, and thus they should not be considered in treating pregnant breast cancer patients.

Data on trastuzumab is limited to 15 pregnant cases with human epidermal growth factor receptor 2 (HER2)-positive breast cancer with a striking high incidence of oligohydramnios reaching up to 50%.[15] This is secondary to the inhibitory effect of trastuzumab on HER2 expressed on the fetal kidney, which is responsible for the amniotic fluid production.[16] Oligohydramnios was mainly observed in patients exposed to the drug for more than 1 trimester.[17] Thus, trastuzumab is strongly discouraged during pregnancy, but if urgently needed, patients should be informed about the potential risks, and close monitoring of the amniotic fluid volume should be carried out. Also, it is advisable to restrict the treatment period to only 1 trimester. As for hormonal therapy, treatment with tamoxifen is contraindicated all through the pregnancy course, because it is associated with a considerable risk of fetal congenital anomalies.[18]

Gynecological tumors Cervical and, less commonly, ovarian cancers have been diagnosed in women during their pregnancy course. Given their anatomical location, their treatment represents a major challenge. Pelvic surgery remains particularly difficult during pregnancy because the access is impaired, and thus an oncologically optimum resection is technically very hard to achieve.[19] Thus, surgery should be considered only in centers with high experience dealing with pregnant cancer patients. On the other hand, radiotherapy should be completely avoided during gestation, in case the mother desires to keep the pregnancy.[8] If such interventions are urgently needed, elective abortion should be considered.

A recent systematic review have identified around 16, 18, and 20 patients treated with chemotherapy for cervical, nonepithelial, and epithelial ovarian cancer, respectively.[8] The coupling of cisplatin with radiotherapy was frequently considered in managing patients with cervical cancer with spontaneous abortion encountered in all patients exposed to radiotherapy. However, cases

exposed to weekly cisplatin alone were associated with normal pregnancy outcome.

For nonepithelial ovarian cancer, 15 in 18 cases did not show any signs of pregnancy complications. In the remaining 3 cases, pregnancy complications were successfully managed with no fetal anomalies documented. The most commonly used regimen was bleomycin, etoposide, and cisplatin, which is considered the gold standard outside pregnancy as well. The combination of paclitaxel and carboplatin was also frequently reported during pregnancy in managing epithelial ovarian cancer with no serious pregnancy complications encountered secondary to in-utero exposure.

Lung cancer The association between lung cancer and pregnancy is very rare, but it is expected to increase due to the increasing rates of cigarette smoking among young women.[20] A recent systematic review of literature performed by our group has identified 44 pregnant women who were diagnosed with lung cancer during pregnancy.[21] The vast majority was diagnosed with adenocarcinoma and had advanced disease. The prognosis was very poor and most of the patients were known to be dead within 1 year following delivery. Only 6 patients were intentionally treated with chemotherapy during gestation with platinum-based chemotherapy. Preterm delivery was observed in 5 of them, which was not unexpected due to the poor maternal condition and high tumor burden associated with these cases.

Several targeted agents were described in managing patients with advanced non-small cell lung cancer.[22] This includes bevacizumab, which is a monoclonal antibody against vascular endothelial growth factor (VEGF) that acts as a key regular of angiogenesis, both physiological (e.g., during embryogenesis and skeletal growth) and pathological (e.g., tumor growth).[23,24] No reports have been described on the use of bevacizumab in pregnant cancer patients. However, given the vital role of angiogenesis in normal development of the fetus, targeting VEGF could result in serious congenital malformations.[15,25,26] Preclinical models using bevacizumab as well as other VEGF tyrosine kinase inhibitors (TKI) were associated with serious pregnancy complications.[24,27] Furthermore, it has been proposed that the "thalidomide tragedy" was secondary to the antiangiogenic effect of thalidomide.[28] Having said that, bevacizumab should not be considered in treating pregnant patients with advanced lung cancer or any other disease. As for epidermal growth factor receptor inhibitors (EGFRI), no reports have been published for cetuximab, while only 1 case was unintentionally exposed to the TKI erlotinib during the first trimester with normal pregnancy outcome.[29] Nevertheless, further data is needed before considering the use of EGFRI during pregnancy.

It is hard to reach a widely accepted approach in managing patients with gestational lung cancer, given the low number of patients identified and their very poor prognosis. Patients should be properly counseled regarding their prognosis and limited available treatment options to make an informed decision to whether or not they are willing to keep their pregnancy. If the patient agreed to proceed with the pregnancy, then the initiation of chemotherapy following the first trimester with a platinum-based combination could be an option. A combination with either paclitaxel or vinorelbine has been described in pregnant lung cancer patients as well as in other settings with good toxicity profile and thus could be considered.

Lymphoma Hodgkin lymphoma (HL) is the most common lymphoma diagnosed during pregnancy. We have recently identified around 70 patients who were treated with systemic chemotherapy during pregnancy.[30] The majority were treated with the standard ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine). Those treated following the first trimester had uneventful pregnancy course and outcome, while, expectedly, there was a high incidence of congenital anomalies in those who were treated with chemotherapy during the first trimester (6/17). Thus, ABVD at standard doses could be considered for pregnant patients diagnosed with HL starting the second trimester. In one report, follow-up of 26 fetuses exposed in-utero to ABVD or MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) until the age of 18 showed normal development with no late toxicities encountered.[31] As for radiotherapy, as previously mentioned and highlighted in the **TABLE**, it could be considered with caution in cases requiring radiotherapy to the neck and/or mediastinal region and in centers with experience in handling these patients. Otherwise, it should be deferred until delivery.

Data on non-Hodgkin lymphoma (NHL) is more or less similar to that of HL. CHOP (cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, and prednisone) was offered to 15 patients with normal pregnancy outcomes.[30] Long-term follow-up for a series of 29 Mexican patients treated with a CHOP-like regimen showed normal development of their infants.[31] Thus, pregnant NHL patients should be considered for CHOP. Radiotherapy could be considered as well in some cases, as previously indicated.

Rituximab is a monoclonal antibody against CD20 and has shown to improve outcomes in indolent and aggressive NHL.[32,33] No preclinical reproductive toxicity models were conducted for rituximab. To date, only 7 lymphoma patients were exposed to rituximab during pregnancy; 6 in combination with chemotherapy, while rituximab was given as a single agent to the 7th patient.[15] The latter had relapsing follicular lymphoma and was exposed unintentionally to rituximab during the first trimester. The drug was stopped and the pregnancy was allowed to continue with normal outcome. The remaining 6 patients had

different types of aggressive NHL and treatment with rituximab was initiated during the second trimester. All 7 patients had unremarkable pregnancy course. However, in 3 of 7 neonates, CD19+ B cells were either undetectable or severely decreased at birth or shortly after.[34-36] The same was observed in another neonate born for a pregnant woman diagnosed with immune thrombocytopenic purpura and treated with rituximab during pregnancy.[37] The condition was reversible in all cases with all B-cell levels returning back to normal within 3 to 6 months. There was no significant postnatal infections encountered and subsequent follow-up revealed adequate response to standard immunization in all 4 children.

Thus, in our opinion, treatment of patients with HL and NHL should not be considerably modified if diagnosis took place during pregnancy. Patients should be treated with standard regimens at routine doses used in the nonpregnant settings. It is important to note that these patients are at a high degree of developing hematological toxicity, and thus adequate monitoring is required. Such toxicities could endanger the pregnancy course and predispose to preterm delivery. Granulocyte colony-stimulating factors (G-CSF) have been reported in only 7 pregnant patients with lymphoma or leukemia with no pregnancy complications encountered.[30] Thus, it could be considered in cases where high risk of neutropenia is anticipated. The same applies for erythropoietin in the management of anemia; however, for the latter blood transfusion remains the preferred choice if possible.

Leukemia Acute leukemias (AL) are more frequently diagnosed during the childbearing period, and indeed they were more frequently described during pregnancy compared to chronic leukemias. Acute myeloid leukemia (AML) is the most common AL diagnosed during pregnancy with more than 100 patients treated with chemotherapy reported in literature.[30]

Outside pregnancy, the combination of cytarabine with either idarubicin or daunorubicin is most commonly used in the treatment of AML during the induction phase.[38] Both combinations were reported during pregnancy with worrying results. Of 32 patients exposed to cytarabine--daunorubicin-based combination following the first trimester, only 15 had normal pregnancy outcome.[30] Around 4 fetal deaths were reported in addition to several congenital anomalies. Similar observations were encountered in 7 patients exposed to idarubicin. The latter is more lipophilic, and thus transplacental transfer is expected to be higher compared to other anthracyclines. Hence, a better alternative during pregnancy could be doxorubicin, for which the data from breast cancer and lymphoma are reassuring. In addition, data on doxorubicin in managing AML outside pregnancy showed comparable efficacy to daunorubicin and idarubicin.[38,39] Several pregnant AML patients were managed with cytarabine in combination with doxorubicin with good fetal outcome.[30]

As for acute lymphoblastic leukemia, similar observations were made regarding the safety of daunorubicin and idarubicin, and thus both should be avoided and replaced by doxorubicin.

Acute promyelocytic leukemia is a subtype of AML and is characterized by the chromosomal translocation t(15/17). It is routinely treated with chemotherapy used in managing AML in addition to all-trans retinoic acid (ATRA) that targets this specific translocation. Around 15 cases were reported to be exposed to single agent ATRA, mainly during the second and third trimester with normal pregnancy outcome.[30] Two cases were exposed to this drug during the first trimester with normal outcome as well. However, preclinical data suggested high risk of anomalies using this agent, and thus it should be avoided early in pregnancy. Hence ATRA could be safely used, and in case chemotherapy is needed, doxorubicin remains the anthracycline of choice as highlighted earlier.

Chronic myeloid leukemia has been also described during pregnancy. It is characterized by the presence of BCR/ABL fusion gene, which is the main driving force for the development and maintenance of the leukemic clone.[40] Targeting this oncogene with imatinib has yielded incredible results leading to curing a large fraction of CML patients.[41] More than 200 patients were exposed to imatinib during pregnancy. Most of the published reports describe cases who got unintentionally pregnant during the treatment course. Early exposure resulted in a high incidence of spontaneous abortion and congenital anomalies reaching up to 30% of reported cases.[30] Those who started imatinib following the first trimester did not encounter pregnancy-related complications. Thus, patients should be advised for contraception while on imatinib. In case pregnancy took place during the treatment course, the drug should be stopped and the patient should be informed on the potential risk of congenital anomalies associated with this drug. If the patient is willing to keep the pregnancy, imatinib should be stopped, and interferon could be considered during the first trimester because it does not cross the placental barrier.[42] Imatinib could be then resumed later during the second trimester.

Conclusions Managing cancer during pregnancy is feasible and safe, provided you administer the right drug at the right time to the right patient. Each patient should be properly counseled and informed that the evidence is scarce to reach a widely agreed decision. Respecting the patient's autonomy is of extreme importance, and the physician's moral judgment should not influence the patient's decision. If the patient decided to preserve the pregnancy and receive active treatment, then the decision should be discussed in a multidisciplinary meeting involving not only the oncology team, but also the obstetrician and

the neonatologist to reach a fairly balanced medical decision acknowledging the potential benefits and risks for both the mother and the fetus.

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ARTYKUŁ POGLĄDOWY

Leczenie nowotworów złośliwych u kobiet w ciąży: na jakich danych naukowych można się oprzeć?

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SŁOWA KLUCZOWE

chemioterapia, nowotwory złośliwe w ciąży, powikłania ze strony płodu, trastuzumab, zaburzenia rozwojowe

STRESZCZENIE

Rozpoznanie nowotworu złośliwego u kobiety w ciąży stanowi bardzo trudny problem kliniczny zarówno z perspektywy chorej, jak i opiekującego się nią lekarza. Ze względu na to, że jest to sytuacja rzadka, dostępne dane naukowe są skąpe, a przeprowadzenie dużych prospektywnych badań klinicznych jest praktycznie niemożliwe. Niezwykle trudnym zagadnieniem jest też potencjalny konflikt między dobrem matki a dobrem płodu: jego konsekwencją może być niewystarczająco agresywne leczenie, spowodowane obawą o toksyczność dla płodu, lub zastosowanie leczenia mogącego wywołać powikłania ze strony płodu lub jego obumarcie. Istnieją pewne wspólne dla wszystkich nowotworów zasady postępowania, jednak każdy rodzaj nowotworu wykazuje swoiste cechy, które należy brać pod uwagę. W tym artykule autorzy starają się przybliżyć dostępne dane naukowe na temat leczenia kobiet ciężarnych chorych na nowotwory złośliwe, tak by dostarczyć pewnych wskazówek lekarzom, którzy spotykają się z takim problemem.

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