Pregnancy-associated Cancer and Chemotherapy during Pregnancy

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The diagnosis of pregnancy-associated cancer, although rare, is a condition of great human and social significance and difficult clinical management. A pregnancy-associated neoplasm is defined as a cancer diagnosis made during pregnancy or within 12 months after delivery/abortion. The most common cancers in pregnancy occur most frequently in women of reproductive age with an incidence overall like that observed in non-pregnant women of the same age. This incidence is likely to increase in view of both the expected increase in certain malignancies among young women (particularly breast cancer and melanoma) and the increasing frequency of pregnancies undertaken later in life (fourth and fifth decades of life) that is characterizing modern society. Chemotherapy is generally contraindicated before 12 weeks of pregnancy due to the increased risk of congenital anomalies while exposure in the second and third trimester of pregnancy to chemotherapy has been associated with more growth restriction and preterm delivery. Clinical decisions about the optimal management should consider maternal and fetal characteristics with the involvement of a multidisciplinary team.

Keywords: Pregnancy-associated cancer, chemotherapy, prematurity.

A pregnancy-associated tumor is defined as a neoplasm that arises during pregnancy or within 12 months of delivery. The incidence of cancers in pregnancy is 1:1000 and increases with increasing maternal age at first pregnancy. The cancers that most frequently develop in pregnancy are those with peak incidence at reproductive age: breast cancer, cervical cancer, ovarian cancer, melanoma, thyroid cancer, lymphomas, and leukemia. In light, however, of the increasing average age at first or subsequent pregnancies, cancers characteristic of later ages (fourth to fifth decades of life) such as lung or colorectal carcinoma may also arise during pregnancy. The development of a tumor during pregnancy presents the clinician with two major challenges: how to set up therapy so that it can benefit the mother without harming the product of conception, and what is the likelihood that the tumor will pass the placenta and may harm the fetus. Although the ways in which tumor cells pass to the placenta or fetus are not perfectly clear to date, in all cases of placental metastasis, tumor...
cells are present in the intervillar spaces. Tumor cells could reach the placenta and fetus via the arterial circulation and the trophoblast could act as a barrier toward tumor invasion. Diagnosis of cancer in pregnancy is often late: in fact, symptoms related to neoplasia are often confused with normal complaints that may occur during this period. Moreover, caregivers are often more reluctant to perform second-tier diagnostic investigations because of the risks to the unborn child, although exposure to them does not appear to result in increased congenital malformations or alterations in cognitive development in children.

**Antineoplastic drugs and pregnancy**

The likelihood of fetal harm associated with the administration of chemotherapeutics during pregnancy is closely related to the gestational age at which exposure occurs, the dose of the drug, its intrinsic characteristics that affect its pharmacokinetics at the placental level (liposolubility, molecular weight, reduced binding to plasma proteins, ionization), and the presence of drug transporters at the placental level, including multidrug resistance proteins and P-glycoprotein. In pregnancy, one faces altered pharmacokinetics related to changes in volume of distribution, rate of metabolism, excretion by the placenta, pH difference between maternal and fetal fluids, and the effect of maternal hemodynamic changes. The change in drug metabolism begins from the fourth week of gestation to increase as pregnancy continues, probably under the influence of progesterone and estrogen. Between the 6th and 34th weeks of gestation, the circulating fluid volume increases by 3-4 liters under the effect of the renin-angiotensin-aldosterone system and antidiuretic hormone, leading to an increase in plasma volume by 1200 ml and red blood cell volume by 300 ml; the total body water volume increases from 5 to 8%.

The dilution of plasma volume results in a reduction in hematocrit and an increase in the concentration of plasma proteins, such as albumin, and there is also a 50% increase in cardiac output. These changes lead to increased hepatic and renal perfusion, resulting in increased glomerular filtration and intrahepatic metabolism, and all of this then leads to reduced concentration of renal and hepatic excreted drugs. At the gastrointestinal level, drug absorption is also altered as a result of changes in gastric secretion and intestinal motility.

All these changes result in a reduction in the plasma concentration of administered drugs based on body surface area. The drugs that most readily cross the placenta by passive diffusion are drugs of low molecular weight (<500 Da), fat-soluble, and not bound to plasma proteins. However, effective concentrations at the placental level are also modulated by different transport proteins. P-glycoprotein (a membrane protein belonging to the ATP-binding-cassette family expressed in the syncytiotrophoblast at the apical level) removes drugs present at the cell membrane and cytoplasm level by preventing toxic substances in the maternal circulation from reaching the fetus.

Breast cancer resistance protein expressed on the apical surface of the syncytiotrophoblast always acts as an active transporter. Also included in the ATP-binding- cassette (ABC) family are ABC proteins C1, 2, 3 or multidrug resistance protein (MRP) 1, 2, 3, transporters of drugs whose concentration varies with gestational age, transcription factors, steroid hormones, and inflammatory pathways. In the syncytiotrophoblast, transporters are present both apically, in contact with the maternal circulation, and on the basolateral membrane, in contact with fetal capillaries. Finally, maternal genetic background may determine different responses in women exposed to the same drug.

Administration of chemotherapy is contraindicated during the first trimester of pregnancy to avoid teratogenic effects: in fact, early exposure increases the risk of major malformations by 10-20%. After the 14th week of gestational age, administration of several chemotherapeutics including taxanes, platinum compounds, anthracyclines, etoposide, and bleomycin is possible. In different studies, the incidence of fetal malformations is comparable to that of the general population, demonstrating the relative safety of chemotherapy administration after the first trimester. To promote the hematologic recovery of the mother and fetus, a time interval of about 21 days between the last cycle of chemotherapy and delivery is necessary to avoid the complications of myelosuppression. Chemotherapy is stopped before three weeks after cesarean delivery and from
35 weeks in a pregnancy with natural childbirth. If weekly administration regimens are used, it can be up to 37 weeks gestational age\(^5\). In addition, breastfeeding during the first few weeks after chemotherapy is not recommended, given the high concentrations of chemotherapeutics that can be reached in breast milk. The drugs most commonly found in breast milk are cyclophosphamide, cyclosporine, doxorubicin and methotrexate and their potential toxic effects are immunosuppression, effect on growth and role in carcinogenesis\(^5\)-\(^7\).

**Chemotherapeutics**

**Natural products: anthracyclines, epipodophyllotoxins, vinca alkaloids, bleomycin, and taxanes**

Anthracyclines, in pregnancy, can be administered from the second trimester of gestation\(^7\). Use during pregnancy would appear to be related to reduced intrauterine growth, prematurity, and reduced and reversible fetal cardiotoxicity, unlike in children and adults, in whom anthracycline use is related to acute and chronic cardiotoxicity\(^3\). These drugs result in fetal cardiac damage, considering that fetal cardiac tissue is susceptible to free radical-induced damage because of the reduced tolerance of cardiomyocytes to changes in the antioxidant-oxidant system and since embryonic and fetal myocytes are smaller than those of adults and their force-generating ability increases only because of the development of contractile proteins and cardiac structural organization\(^4\).

Reduced ventricular wall thickness and ventricular mass index were observed in acute studies, while ventricular shortening fraction, ejection fraction, and intraventricular thickness at the lower limits of normal were observed in the five-year follow-up. However, studies on chronic cardiotoxicity related to anthracycline use in pregnancy are absent\(^1\). It should also be mentioned that during pregnancy the metabolism of anthracyclines is increased because of increased cytochrome P-450 3A4 activity during the third trimester\(^2\). Because anthracyclines have a molecular weight >500 Da and bind plasma proteins, they presumably exhibit reduced transplacental passage, and furthermore, between doxorubicin and epirubicin, the latter exhibits less transplacental passage, making it less toxic to the placenta than doxorubicin. Idarubicin, on the other hand, is more lipophilic and binds less to P-glycoprotein, thus presenting greater transplacental passage and greater toxicity.

To reduce the toxicity of doxorubicin, liposomal, nonpegylated, and pegylated formulations of doxorubicin have been introduced, among which the pegylated form is the one characterized by less transplacental passage. Doxorubicin and epirubicin can be used from the second trimester onward being burdened with minimal teratogenic risk; however, as for idarubicin, this should be prescribed only when there are no alternatives and always with caution. From the point of view of cardiotoxicity, idarubicin and daunorubicin are related to cardiac dilatation, myocardial hypertrophy, coronary artery dilatation, moderate atrial and right ventricular dilatation with moderate reduction in function, atrial septal defect of ostium secundo type, and patency of the ductus arteriosus. However, these changes tend to resolve in the long term.

In contrast, doxorubicin and epirubicin have a good safety profile, being unrelated in most cases, to cardiac alterations, such as changes in ventricular diameters, septal thickness, ejection fraction, and shortening fraction. Regarding the assessment of late cardiotoxicity on infants exposed to anthracyclines during fetal life, the gold standard is the shortening fraction assessed in two-dimensional echocardiography. In contrast, at the neurological level, no anthracycline-induced alterations have been shown. In any case, although the data on anthracycline-related cardiotoxicity and neurotoxicity argue in favor of the absence of side effects, long-term follow-up of children exposed in utero to these drugs still proves necessary. Of paramount importance during the administration of anthracyclines is the evaluation of concomitant drugs that may inhibit P-glycoprotein and thus promote its increased passage at the placental level: in particular, it has been shown how the administration of glucocorticoids to prevent pulmonary immaturity by reducing P-glycoprotein expression can result in increased epirubicin-related toxicity\(^4\).

Etoposide is the only compound of the epipodophyllotoxin family used in pregnancy. In the mother, this drug results in dose-limiting myelosuppression, prolongation of prothrombin time and International Normalized Ratio (INR). In
the fetus, no malformations have been shown, but there is a possibility of reduced intrauterine growth and neonatal pancytopenia.

Bleomycin can result in dose-dependent pneumonias in the mother, while in the fetus no birth defects determined by administration of this drug during pregnancy have been shown.\textsuperscript{76,77} Vincristine has a good safety profile when administered during pregnancy. Little evidence is available for the other drugs in this class.\textsuperscript{76}

Taxanes, used mainly in the treatment of breast and ovarian cancer, have a good safety profile in pregnancy when administered from the second trimester onward. Indeed, they are fairly safe drugs as substrates of P-glycoprotein, which prevents their entry into the fetal compartment.\textsuperscript{78,79}

Alkylating agents

Cyclophosphamide results in side effects in both mother and fetus. In the mother, there is dose-dependent myelosuppression; in the fetus, however, if cyclophosphamide is administered during the first trimester, there may be fetuses without malformations or the presence of oculofacial malformations, finger agenesis or nail changes, coronary artery defects, umbilical hernia, hemangiomias, imperforate anus, rectovaginal fistula, cleft palate, microcephaly, impaired growth, and developmental delay. In contrast, if cyclophosphamide is administered during the second and third trimesters, there is no risk of malformations, but there is a risk of reduced intrauterine growth, microcephaly, and neonatal pancytopenia. Dacarbazine may result in dose-dependent myelosuppression in the mother; in the fetus, however, it has demonstrated a good safety profile when administered during the second and third trimesters together with other drugs such as carmustine and cisplatin.\textsuperscript{76}

Platinum compounds

Platinum compounds have a good safety profile when administered in pregnancy, given the low concentration of drug that crosses the placenta.\textsuperscript{77,80} Mir et al. in their study showed that the transplacental passage of cisplatin and carboplatin increases with advancing gestational age. Cisplatin and carboplatin correlate with specific effects on the fetus.\textsuperscript{81} Cisplatin is related to impaired endouterine growth, respiratory distress syndrome, bilateral ventriculomegaly, nephrotoxicity, ototoxicity, and bone marrow suppression. Because of drug-related ototoxicity, cisplatin can be substituted by carboplatin, burdened with less toxicity. Carboplatin, because of its high free fraction and low molecular weight, crosses the placenta. However, it is used in pregnant women with gynecological cancers, presenting a good safety profile.\textsuperscript{59,82} From the point of view of follow-up of the unborn child, following intrauterine exposure to platinum compounds, an assessment of auditory function by Auditory Brainstem Response (ABR)/Otoacoustic Emissions (OAE) is recommended up to 6 years of age and by an audiogram thereafter.\textsuperscript{89}

Monoclonal antibodies

Rituximab is an IgG1-class antibody directed against the CD20 antigen, which is present on the surface of normal and pathological B lymphocytes. When administered during pregnancy, Rituximab may result in a reduction in the concentration of B lymphocytes in the unborn child. Attention should therefore be paid to the risk of neonatal and postnatal cytopenias dependent on this drug, resulting in an increased risk of infection.\textsuperscript{83-87} For infants exposed during fetal life to rituximab, monitoring in the 12 months after birth with serial complete blood count examinations and evaluation of different immunoglobulin subclasses is useful. Indeed, cases of IgG, IgM and IgA depletion in children exposed to Rituximab during intrauterine life have been reported in the literature, although in all cases there was complete resolution of the deficiency and absence of long-term effects.\textsuperscript{88,89}

### Table 1. Pregnancy risk of some common targeted and immunotherapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy/neonatal complication</th>
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</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Neonatal B-cell depletion</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Not associated</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Possibly pre-eclampsia</td>
</tr>
<tr>
<td>PD-1/PD-L1 inhibitors</td>
<td>Abortion, miscarriage, fetal growth restriction, and prematurity</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Oligohidramnios</td>
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</tbody>
</table>
Biologic drugs

Interferon-α is a valuable treatment for pregnant melanoma and chronic myeloid leukemia patients. This drug does not cross the placental barrier in significant concentrations and therefore is not considered nocive to the fetus.88

Hormone therapies, and Immune check point inhibitors

Hormone therapy, targeted therapy, and radiotherapy are discouraged during the period of pregnancy because they can harm the baby by interfering with its development and are therefore not usually administered during pregnancy.

Administration of immune checkpoint inhibitors during pregnancy is associated with an increased incidence of pregnancy complications, including miscarriage, fetal growth restriction, and prematurity. Therefore, administration of these regimens is not recommended during gestation. Whenever they are administered, close monitoring of the mother and fetus is necessary (Table 1).

However, it is notoriously difficult to study the effects of drugs that occur even years after their use, in a scenario of rapidly changing clinical practice and a large number of pharmacological changes. Confusion with treatment indications is an inherent problem that can only be adequately resolved by large, well-designed clinical trials.88,89

Radiotherapy

The risk related to radiotherapy depends on the absorbed dose and gestational age.90-92 Radiation therapy has different side effects for the fetus, such as reduced intrauterine growth, congenital malformations, mental retardation, and carcinogenesis. Specifically, doses <0.1 Gy do not result in effects (the incidence of fetal abnormalities following exposure to these doses is comparable to the incidence of fetal congenital abnormalities), doses between 0.1-0.15 Gy result in an increased risk of malformations, doses of 2.5 Gy result in malformations in most cases, and doses > 30 Gy abortion. On the other hand, with regard to administration at different stages of gestation, if radiotherapy is given within the first 10 days after conception, its effect is lethal, between 2- and 12-weeks malformations can develop in most cases and growth retardation, between 13 and 16 weeks cognitive and growth retardation, and between 17- and 26-weeks neoplasia, infertility, and genetic defects [93-99]. One of the stochastic (i.e., fortuitous, and nondose-dependent) effects is an increased incidence of neoplasms in pediatric age, especially leukemia, regardless of gestational age of exposure.82,100-104

Surgery

Surgery is sometimes part of cancer treatment. Surgery, if necessary, can be safely performed at any time during pregnancy. However, an increased risk of miscarriage has been reported when performed in the first trimester. In addition, the risk of small fetuses for gestational age is reported when a pregnant patient undergoes a lengthy abdominal procedure during the period of pregnancy. In addition, major abdominal and pelvic surgery is associated with increased morbidity and pregnancy complications, such as preterm delivery, throughout the gestation period. Therefore, a watchful waiting policy may also be considered. However, when the patient is at high risk for torsion (usually at gestational week 8-16), rupture infarction, or acute abdomen, surgical management is indicated.

It is generally considered that surgery is safer if performed in the second or early third trimester, although the second trimester is still preferred. However, surgery should never be postponed if it is deemed crucial to the management of the patient.

The type of surgery depends on the extent of the tumor, its location, and the time at which it is diagnosed. If tumor size and site allow, it is preferable to use local anesthesia, or laparoscopic surgery. Laparoscopic surgery usually results in less blood loss, less pain, shorter recovery time, and fewer preterm contractions than open surgery.

CONCLUSIONS

In the literature, more authors are reporting the administration of chemotherapy during the second and third trimesters of pregnancy as relatively safe, although cases of accidental administration during the first trimester with favorable neonatal outcome are also reported. The diagnosis of cancer in pregnancy poses two major challenges: preserving the health of the mother, including administering chemotherapy when necessary, and safeguarding the health of the baby.

In cases where it has been possible (indolent, low-grade disease), efforts have been
made to continue the pregnancy and postpone treatment in the postpartum period, scheduling the baby’s birth as close to term as possible. In this way, the fetus was not exposed to any side effects of chemotherapy and the mother was able to receive a full-dose treatment regimen. In both cases, placental histologic examination turns out to be of paramount importance to assess the absence of metastases at the placental level. Prematurity, related to maternal conditions, is a condition of paramount importance considering the complications that may be related to it, such as hyaline membrane disease, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, hypoglycemia, feeding difficulties, but also long-term complications, such as an increased risk of neonatal death or complications affecting the child’s neuro-cognitive and behavioral development.

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Conflict of Interests

The authors declare no competing interests.

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REFERENCES

In this study, we aimed to investigate the effects of chemotherapy in pregnant women with cancer. We conducted a systematic review on the use of cytotoxic, endocrine, and targeted agents and immunotherapy during pregnancy. Part I: Solid tumors.

We found that chemotherapy during pregnancy may offer safe cardiac and neurodevelopmental outcomes for the developing fetus. However, the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy is a concern.

We also assessed the risks and benefits of using newer antiseizure medications in pregnant women. Our findings suggest that lacosamide may be a safer alternative for women with multiple sclerosis.

Overall, our study highlights the importance of considering the risks and benefits of chemotherapy in pregnant women with cancer. Further research is needed to improve outcomes for both the mother and the developing fetus.


