Biomedical & Pharmacology Journal, June 2023. Vol. **16**(2), p. 705-714

Pregnancy-associated Cancer and Chemotherapy during Pregnancy

Alberto Romano, Stefano Mastrangelo, Giorgio Attina', Palma Maurizi and Antonio Ruggiero

Pediatric Oncology Unit, Fondazione Policlinico Universitario A.Gemelli IRCCS, Universita' Cattolica Sacro Cuore, Rome, Italy.
*Corresponding author E-mail: antonio.ruggiero@unicatt.it

https://dx.doi.org/10.13005/bpj/2652

(Received: 15 April 2023; accepted: 06 June 2023)

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[1]. 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[2-13]. 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 intervillary spaces[14-17]. Tumor cells could reach the placenta and fetus via the arterial circulation and the trophoblast could act as a barrier toward tumor invasion[18]. 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[19-29].

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[30,31]. 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[32-41].

All these changes result in a reduction in the plasma concentration of administered drugs based on body surface area[42,43]. 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[44]. Finally, maternal genetic background may determine different responses in women exposed to the same drug[2,3,45-48].

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[49-57]. 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[2,31]. 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[58]. 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[59-73].

Chemotherapeutics

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

Anthracyclines, in pregnancy, can be administered from the second trimester of gestation[74,75]. 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[30]. 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[44].

Reduced ventricular wall thickness and ventricular mass index were observed in acute studies, while ventricular shortening fraction, ejection fraction, and interventricular 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[30]. 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[42]. 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 secondo 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 epirubicline-related toxicity[44].

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[76,77]. Vincristine has a good safety profile when administered during pregnancy. Little evidence is available for the other drugs in this class[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[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, hemangiomas, 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[76].

Platinum compounds

Platinum compounds have a good safety profile when administered in pregnancy, given the low concentration of drug that crosses the placenta[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[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[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[59].

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[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[88,89].

Table 1. Pregnancy risk of some common targeted and immunotherapies

Drug	Pregnancy/neonatal complication
Rituximab	Neonatal B-cell depletion
Imatinib	Not associated
Bevacizumab	Possibly pre-eclampsia
PD-1/PD-L1 inhibitors	Abortion, miscarriage, fetal growth restriction, and prematurity
Trastuzumab	Oligohidramnios

Biologic drugs

Interferon-á 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.

ACKNOWLEDGMENTS

The authors thank "Fondazione per l'Oncologia Pediatrica ONLUS" for their dedicated patient care and scientific support.

Conflict of Interests

The authors declare no competing interests.

Funding Sources

There is no funding Sources

REFERENCES

1. Melan K, Volumenie J, Wan-Ajouhu G et al. Pregnancy-associated-cancer in the French West Indies (Martinique): maternal and neonatal outcomes. *BMC Pregnancy Childbirth.* 2017;17(1):334.
2. Sood AK, Shahin MS, Sorosky JI. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol.* 2001;83(3):599–600.
3. Zheng X, Zhu Y, Zhao Y et al. Taxanes in combination with platinum derivatives for the treatment of ovarian cancer during pregnancy: a literature review. *Int J Clin Pharmacol Ther*. 2017;55:753–760.
4. Brewer M, Kueck A, Runowicz CD. Chemotherapy in Pregnancy. *Clin Obstet Gynecol*. 2011;54(4):602-18.
5. Zagouri F, Dimitrakakis C, Marinopoulos S et al. Cancer in pregnancy: disentangling treatment modalities. *ESMO Open*. 2016;1(3):e000016.
6. Van Calsteren K, Heyns L, De Smet F et al. Cancer during pregnancy: an analysis of 215 patient emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol*. 2010;28(4):683-9.
7. Li SS, Hsu YT, Yen CC, et al. Maternal survival of patients with pregnancy-associated cancers in Taiwan - A national population-based study. *Cancer Med*. 2020(24):9431-9444.
8. Dalmartello M, Negri E, La Vecchia C, et al. Frequency of Pregnancy-Associated Cancer: A Systematic Review of Population-Based Studies. *Cancers (Basel)*. 2020;12(6):1356.
9. Parazzini F, Gadducci A, Cicinelli E, et al. Pregnancy-associated cancers: frequency and temporal trends in Italy. *Int J Gynecol Cancer.* 2020;30(2):241-244.
10. Cottreau CM, Dashevsky I, Andrade SE, et al. Pregnancy-Associated Cancer: A U.S. Population-Based Study. *J Womens Health (Larchmt)*. 2019;28(2):250-257.
11. Troisi R, Bjørge T, Gissler M, et al. The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence. *J Intern Med.* 2018;283(5):430-445.
12. Melan K, Volumenie JL, Wan-Ajouhu G, Ulric-Gervaise S, Veronique-Baudin J, Joachim C. Pregnancy-associated-cancer in the French West Indies (Martinique): maternal and neonatal outcomes. *BMC Pregnancy Childbirth.* 2017;17(1):334.
13. Balaya V, Bonsang-Kitzis H, Ngo C, et al. What about sentinel lymph node biopsy for early breast cancer during pregnancy? *J Gynecol Obstet Hum Reprod.* 2018;47(5):205-207.
14. Vale Bezerra PK, Chaves Cavalcanti JE, et al. Drug-related problems in hypertension and gestational diabetes mellitus: A hospital cohort. *PLoS One*. 2023;18(4):e0284053.
15. Mino R, Shimada H, Wakiya R, et al. Pregnancy course and outcomes of patients with polymyositis and dermatomyositis (PM/DM) managed in a single center. *Medicine (Baltimore).* 2023;102(14):e33462.
16. Lundholm MD, Marquard J, Rao PP. Paraganglioma in pregnancy, a mimic of preeclampsia: a case report. *J Med Case Rep*. 2023;17(1):124.
17. Tremblay E, Pina A, Avon-Després C, Mercier F, Cormier B. Hyperthermic Intraperitoneal Chemotherapy and Interval Debulking Surgery in Conjunction With Elective Cesarean Delivery. *Obstet Gynecol*. 2023 Apr 6. doi:10.1097/AOG.0000000000005146.
18. Jackisch C, Louwen F, Schwenkhagen A, et al. Lung cancer during pregnancy involving the products of conception and a review of the

literature. *Arch Gynecol Obstet*. 2003;268(2):69-77.

19. Boussios S, Han SN, Fruscio R et al. Lung cancer in pregnancy: report of nine cases from an international collaborative study. *Lung Cancer*. 2013;82(3):499-505.
20. Pavlidis N. Lung cancer during pregnancy. An emerging issue. *Lung Cancer*. 2008; 59(3):279-81.
21. Jhaveri MB, Driscoll MS, Grant-Kels JM. *Melanoma in Pregnancy*. 2011;54(4):537-45.
22. Menzer C, Beedgen B, Rom J, et al. Immunotherapy With Ipilimumab Plus Nivolumab in a Stage IV Melanoma Patient During Pregnancy. *Eur J Cancer.* 2018;104:239-242.
23. Chiaretti A, Conti G, Falsini B, Buonsenso D, Crasti M, Manni L, et al. Intranasal Nerve Growth Factor administration improves cerebral functions in a child with severe traumatic brain injury: A case report. *Brain Inj*. 2017;31(11):1538-1547.
24. Froehlich K, Stensheim H, Markert UR, Turowski G. Breast carcinoma in pregnancy with spheroid-like placental metastases — a case report. *APMIS*. 2018;126(5):448-452.
25. Timeus F, Crescenzio N, Longoni D, et al. Paroxysmal nocturnal hemoglobinuria clones in children with acquired aplastic anemia: a multicentre study. *PLoS One*. 2014;9(7):e101948.
26. Morton SK, Morton AP. Melanoma and Pregnancy. *Australas J Dermatol*. 2017;58(4):259-267.
27. Azim Jr HA, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. *Cancer Treat Rev.* 2010;36(2):101-9.
28. Chiaretti A, Ruggiero A, Barbi E, et al. Comparison of propofol versus propofol-ketamine combination in pediatric oncologic procedures performed by non-anesthesiologists. *Pediatr Blood Cancer*. 2011;57(7):1163-1167
29. Murthy RK, Theriault RL, Barnett CM. Outcomes of children exposed in utero to chemotherapy for breast cancer. *Breast Cancer Res.* 2014;16(6):500.
30. Amant F, Han SN, Gziri MM, et al. Chemotherapy during pregnancy. *Curr Opin Oncol*. 2012;24(5):580-6.
31. Esposito S, Tenconi R, Preti V, et al. Chemotherapy against cancer during pregnancy. A systematic review on neonatal outcomes. *Medicine (Baltimore)*. 2016;95(38):e4899.
32. Andrade C. Gestational Exposure to Benzodiazepines and Z-Hypnotics and the Risk of Major Congenital Malformations, Ectopic Pregnancy, and Other Adverse Pregnancy Outcomes. *J Clin Psychiatry.* 2023;84(2):23f14874.
33. Riccardi A, Mazzarella G, Cefalo G, et al. Pharmacokinetics of Temozolomide given three times a day in pediatric and adult patients. *Cancer Chemother Pharmacol.* 2003; 52: 459-464
34. Abrams M, Magun E, DeFilippis EM. Considerations for specific cardiomyopathies during pregnancy. *Curr Opin Cardiol*. 2023;38(3):233-240.
35. Lazzareschi I, Ruggiero A, Riccardi R, Attinà G, Colosimo C, Lasorella A. Hypersensitivity reactions to carboplatin in children. *J Neurooncol.* 2002; 58:33-37
36. Haker MC, Frahm N, Hecker M, et al. Therapy of women with multiple sclerosis: an analysis of the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy. *Ther Adv Drug Saf*. 2023;14:20420986221143830.
37. Chiaretti A, Aloe L, Antonelli A, et al. Neurotrophic factor expression in childhood low-grade astrocytomas and ependymomas. *Childs Nerv Syst.* 2004; 20:412-419
38. Zhang L, Liu C, Xiao L, Liu Y. Low-dose methotrexate-induced renal failure in a patient with ectopic pregnancy: a case report. *J Med Case Rep.* 2023;17(1):119.
39. Trisciuzzi MT, Riccardi R, Piccardi M, et al. A fast visual evoked potential method for functional assessment and follow-up of childhood optic gliomas. *Clin Neurophysiol*. 2004; 115: 217-226
40. Hoeltzenbein M, Slimi S, Fietz AK, et al. Increasing use of newer antiseizure medication during pregnancy: An observational study with special focus on lacosamide. *Seizure*. 2023;107:107-113
41. Falsini B, Chiaretti A, Barone G, et al. Topical nerve growth factor as a visual rescue strategy in pediatric optic gliomas: a pilot study including electrophysiology. *Neurorehabil Neural Repair.* 2011; 25: 512-520.
42. Boere I, Lok C, Vandenbroucke T, Amant F. Cancer in pregnancy: safety and efficacy of systemic therapies. *Curr Opin Oncol*. 2017; 29(5):328-334.
43. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*. 2004;5(5):283-91.
44. Framarino-Dei-Malatesta M, Sammartino P, Napoli A. Does anthracycline-based chemotherapy in pregnant women with cancer offer safe cardiac and neurodevelopmental outcomes for the developing fetus? *BMC Cancer*.

2017;17(1):777
45. Ruggiero A, Rizzo D, Catalano M, Coccia P, Triarico S, Attiná G. Acute chemotherapy-induced nausea and vomiting in children with cancer: Still waiting for a common consensus on treatment. *J Int Med Res*. 2018;46(6):2149-2156.
46. Ruggiero A, Rizzo D, Trombatore G, Maurizi P, Riccardi R. The ability of mannitol to decrease cisplatin-induced nephrotoxicity in children: real or not?. *Cancer Chemother Pharmacol*. 2016;77(1):19-26.
47. Ruggiero A, Rizzo D, Mastrangelo S, Battaglia D, Attinà G, Riccardi R. Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: is it time to change treatment?. *Pediatr Blood Cancer*. 2010;54(2):193-198
48. Falsini B, Ziccardi L, Lazzareschi I, et al. Longitudinal assessment of childhood optic gliomas: relationship between flicker visual evoked potentials and magnetic resonance imaging findings. *J Neurooncol*. 2008; 88: 87-96.
49. Cummings M, Edmonds P, Shahin MS, Sorosky JI. Juvenile granulosa cell tumor in an adult woman during pregnancy: A case report and review of the literature. *Gynecol Oncol Rep*. 2023;46:101164.
50. Ruggiero A, Barone G, Liotti L, Chiaretti A, Lazzareschi I, Riccardi R. Safety and efficacy of fentanyl administered by patient controlled analgesia in children with cancer pain. *Support Care Cancer*. 2007;15(5):569-73. doi: 10.1007/s00520-006-0193-8.
51. Takeda M, Kataoka A, Abe T, et al. Childbirth after perioperative systemic therapy in patients with breast cancer: a retrospective single institutional study in Japan. Jpn J Clin Oncol. 2023 Mar 27:hyad023. doi:10.1093/jjco/hyad023.
52. Ruggiero A, Maurizi P, Larocca LM, Arlotta A, Riccardi R. Childhood CD4+/CD56+ hematodermic neoplasm: case report and review of the literature. Haematologica. 2006;91(12 Suppl):ECR48.
53. Tan MY, Shu SH, Liu RL, Zhao Q. The efficacy and safety of complementary and alternative medicine in the treatment of nausea and vomiting during pregnancy: A systematic review and meta-analysis. Front Public Health. 2023;11:1108756.
54. Posteraro B, Bruno S, Boccia S, et al. Candida parapsilosis bloodstream infection in pediatric oncology patients: results of an epidemiologic investigation. Infect Control Hosp Epidemiol. 2004;25(8):641-5.
55. Lundberg FE, Gkekos L, Rodriguez-Wallberg KA, Fredriksson I, Johansson ALV. Risk of obstetric and perinatal complications in women presenting with breast cancer during pregnancy and the first year postpartum in Sweden 1973-2017: A population-based matched study. Acta Obstet Gynecol Scand. 2023 Mar 23. doi:10.1111/aogs.14555.
56. Chiaretti A, Ruggiero A, Barone G, et al. Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. Eur J Cancer Care. (Engl) 2010;19(2):212-220
57. Sellami I, Beau I, Sonigo C. Chemotherapy and female fertility. Ann Endocrinol (Paris). 2023 Mar 24:S0003-4266(23)00063-X. doi:10.1016/j.ando.2023.03.013.
58. Brewer M, Kueck A, Runowicz CD. Chemotherapy in Pregnancy. Clin Obstet Gynecol. 2011;54(4):602-18.
59. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019;30(10):1601-1612
60. Xu W, Moor RJ, Walpole ET, Atkinson VG. Pregnancy With Successful Foetal and Maternal Outcome in a Melanoma Patient Treated With Nivolumab in the First Trimester: Case Report and Review of the Literature Melanoma Res. 2019;29(3):333-337.
61. Ruggiero A, Rizzo D, Attinà G, et al. Phase I study of temozolomide combined with oral etoposide in children with recurrent or progressive medulloblastoma. Eur J Cancer. 2010;46(16):2943-9.
62. Burotto M, Gormaz JG, Samtani S et al. Viable Pregnancy in a Patient With Metastatic Melanoma Treated With Double Checkpoint Immunotherapy Semin Oncol. 2018;45(3):164-169.
63. Ferrara P, Marrone G, Emmanuele V, et al. Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial. Pediatr Nephrol. 2008;23(2):269-274.
64. Yust-Katz S, de Groot JF, Liu D et al. Pregnancy and glial brain tumors. Neuro Oncol. 2014;16(9):1289-94.
65. Falsini B, Iarossi G, Chiaretti A, et al. NGF eye-drops topical administration in patients with retinitis pigmentosa, a pilot study. J Transl Med. 2016;14:8.
66. Zwinkels H, Dörr J, Kloet F, Taphoorn MJB, Vecht CJ. Pregnancy in women with gliomas: a case-series and review of the literature. J Neurooncol. 2013;115(2):293-301.
67. Triarico S, Romano A, Attinà G, et al. Vincristine-

Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. Int J Mol Sci. 2021;22(8):4112. doi: 10.3390/ijms22084112.
68. van Westrhenen A, Senders JT, Martin E, et al. Clinical challenges of gliomas and pregnancy: a systematic review. J Neurooncol. 2018;139(1):1-11.
69. Romano A, Capozza MA, Mastrangelo S, et al. Assessment and Management of Platinum-Related Ototoxicity in Children Treated for Cancer. Cancers (Basel). 2020;12(5):1266.
70. Gurcay AG, Bozkurt I, Senturk S, et al. Diagnosis, Treatment, and Management Strategy of Meningioma during Pregnancy. Asian J Neurosurg. 2018;13(1):86-89
71. Fetoni AR, Ruggiero A, Lucidi D, et al. Audiological Monitoring in Children Treated with Platinum Chemotherapy. Audiol Neurootol. 2016;21(4):203-211.
72. Chakravarthy V, Kaplan B, Gospodarev V, et al. The Houdini Tumor: A Case Report and Literature Review of Pregnancy Associated Meningiomas. World Neurosurg. 2018;114:e1261-e1265.
73. Laviv Y, Bayoumi A, Mahadevan A, et al. Meningiomas in pregnancy: timing of surgery and clinical outcomes as observed in 104 cases and establishment of a best management strategy. Acta Neurochir (Wien). 2018;160(8):1521-1529.
74. Gziri MM, Debiève F, De Catte L. Chemotherapy during pregnancy: effect of anthracyclines on fetal and maternal cardiac function. Acta Obstet Gynecol Scand. 2012;91(12):1465-8.
75. Beksac K, Orgul G, Ozyuncu O, et al. Chemotherapy during Pregnancy: Cases of Hodgkin's and Non-Hodgkin's Lymphoma, Chronic Myeloid Leukemia, Breast Cancer, Nasopharyngeal Cancer, and Choriocarcinoma. Oncol Res Treat. 2017;40(7-8):441-445.
76. Leslie KK, Koil C, Rayburn WF. Chemotherapeutic Drugs in Pregnancy. Obstet Gynecol Clin North Am. 2005;32(4):627-40.
77. Figueredo de Oliveira A, Marquez Ferreira de Souza LR, Carvalho Paschoini M, et al. Chemotherapy for cervical cancer in pregnancy. J Obstet Gynaecol. 2019;39(3):425-426.
78. Berveiller P, Mir O. Taxanes during Pregnancy: Probably Safe, but Still to Be Optimized. Oncology. 2012;83(4):239-40.
79. Cardonick E, Bhat A, Gilmandyar D, Somer R. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. Ann Oncol. 2012;23(12):3016-23.
80. Sofia R, Melita V, De Vita A, et al. Cardiac Surveillance for Early Detection of Late Subclinical Cardiac Dysfunction in Childhood Cancer Survivors After Anthracycline Therapy. Front Oncol. 2021;11:624057.
81. Mir O, Berveiller P, Ropert S, et al. Use of Platinum Derivatives During Pregnancy. Cancer. 2008;113(11):3069-74.
82. Vandenbroucke T, Verheecke M, Fumagalli M, et al. Effects of cancer treatment during pregnancy on fetal and child development. Lancet Child Adolesc Health. 2017;1(4):302-310.
83. Azim HA Jr, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. Cancer Treat Rev. 2010;36(2):110-21.
84. Moshe Y, Bentur OS, Lishner M, Avivi I. The management of Hodgkin lymphomas in pregnancies. Eur J Haematol. 2017;99(5):385-391.
85. Mandal PK, Dolai TK, Bagchi B, et al. B cell suppression in newborn following treatment of pregnant diffuse large b-cell lymphoma patient with rituximab containing regimen. Indian J Pediatr. 2014;81(10):1092-4.
86. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117(5):1499-506.
87. Decker M, Rothermundt C, Holländer G, et al. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. Lancet Oncol. 2006;7(8):693-4.
88. Lambertini M, Peccatori FA, Azim HA Jr. Targeted agents for cancer treatment during pregnancy. Cancer Treat Rev. 2015;41(4):301-9.
89. Andrikopoulou A, Korakiti AM, Apostolidou K, Dimopoulos MA, Zagouri F. Immune checkpoint inhibitor administration during pregnancy: a case series. ESMO Open. 2021;6(5):100262.
90. Harwin J, Jha P, Post A, Silverstein J, Van Loon K, Poder L. The radiologist's role in a multidisciplinary approach to cancer in pregnancy. Abdom Radiol (NY). 2023 Jan 27. doi: 10.1007/s00261-023-03809-0.
91. Javitt MC. Cancer in pregnancy: overview and epidemiology. Abdom Radiol (NY). 2022 Aug 12. doi: 10.1007/s00261-022-03633-y.
92. Jha P, Pôder L, Glanc P, et al. Imaging Cancer in Pregnancy. Radiographics. 2022;42(5):1494-1513.
93. Luis SA, Christie DRH, Kaminski A. Pregnancy and radiotherapy: Management options for minimising risk, case series and comprehensive literature review. J Med Imaging Radiat Oncol. 2009;53(6):559-68

94. Abdelnabi M, Cavazos A, Thongpiya J, et al. Acute Onset of Bullous Skin Rash and Acute Kidney Injury after Exposure to Radiocontrast: Sweet's Syndrome. Eur J Case Rep Intern Med.2023;10(4):003781.
95. Sivaranjani P, Arora A, Suri V. Unintended pregnancies during cancer therapy requiring pregnancy termination: Can these be avoided? Indian J Public Health. 2022;66(4):533.
96. Graham EL. Neuroimmunological Disorders: The Gender Effect. Neurol Clin. 2023;41(2):315-330.
97. Saad M, Murphy MSQ, McGee SF, El-Chaâr D. Pregnancy and neonatal outcomes following malignancy in pregnancy at a tertiary care Canadian center: a retrospective chart review. J Matern Fetal Neonatal Med. 2023;36(1):2198631.
98. Cairncross ZF, Shack L, Nelson G, et al. Long-term Mortality in Individuals Diagnosed With Cancer During Pregnancy or Postpartum. JAMA Oncol. 2023 Apr 6:e230339. doi:10.1001/jamaoncol.2023.0339.
99. Safi N, Li Z, Anazodo A, Remond M, et al. Pregnancy associated cancer, timing of birth and clinical decision making-a NSW data linkage study. BMC Pregnancy Childbirth. 2023;23(1):105.
100. Greiber IK, Viuff JH, Mellemkjaer L, et al. Cancer in pregnancy and the risk of adverse pregnancy and neonatal outcomes: A nationwide cohort study. BJOG. 2022;129(9):1492-1502.
101. Mellemkjær L, Eibye S, Albieri V, Kjær SK, Boice JD Jr. Pregnancy-associated cancer and the risk of second primary cancer. Cancer Causes Control. 2022;33(1):63-71.
102. Johansson ALV, Fredriksson I, Mellemkjaer L, et al. Cancer survival in women diagnosed with pregnancy-associated cancer: An overview using nationwide registry data in Sweden 1970-2018. Eur J Cancer. 2021;155:106-115.
103. Metcalfe A, Cairncross ZF, Friedenreich CM, et al. Incidence of Pregnancy-Associated Cancer in Two Canadian Provinces: A Population-Based Study. Int J Environ Res Public Health. 2021;18(6):3100.
104. Esposito G, Franchi M, Dalmartello M, et al. Obstetric and neonatal outcomes in women with pregnancyassociated cancer: a population-based study in Lombardy, Northern Italy. BMC Pregnancy Childbirth. 2021;21(1):31.
105. Proussaloglou EM, Blanco LZ Jr, Siziopikou KP. Updates in the pathology of Pregnancy Associated Breast Cancer (PABC). Pathol Res Pract. 2023;244:154413.