Malignancies Diagnosed During Pregnancy and Treated With Chemotherapy or Other Modalities (Review of 27 Cases)

Multicenter Experiences

Anatolian Medical Oncology Society Group

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Background: Cancer is the second leading cause of death in women of reproductive age. The most common tumors diagnosed during pregnancy are breast and cervix cancer, Hodgkin lymphoma and non-Hodgkin lymphoma, leukemias, and malignant melanoma. The aim of therapy in pregnancy is to give optimal treatment to the mother without harm to the fetus. In the first trimester, organogenesis continues, so chemotherapy should not be given because of increasing risk of spontaneous abortion, fetal malformation, and mortality. We evaluated mostly seen tumors during pregnancy and assessed treatment type and outcome of pregnancy after chemotherapy in our population.

Methods: We retrospectively analyzed 27 patients who have been treated during pregnancy or after the delivery because of several malignancies.

Results: The tumors associated with pregnancy were breast cancer, hematologic malignancies, gynecologic malignancies, sarcomas, and others. The chemotherapy regimens were given in 17 of 27 patients in the second or third trimester of pregnancy. Four of the patients were diagnosed with cervical cancer, hemangiopericytoma, chronic myeloid leukemia, and breast cancer during the first trimester, so their pregnancies were ended by therapeutic abortion. Although 1 of the 3 fetuses who were exposed to chemotherapy in utero at the second or third trimester was born prematurely and low birth weight was diagnosed in the other 2 fetuses, fetal malformation was not seen in any of them. There were 7 normal and 9 cesarean deliveries. Twenty-three healthy babies survived from 27 pregnancies, of whom 17 babies were exposed to chemotherapeutic agents.

Conclusions: We reported herein 27 patients with malignancies diagnosed during pregnancy; 17 patients received chemotherapy during the gestational period without any fetal or maternal abnormalities. Because of the low incidence of malignancy during pregnancy, our report is noteworthy.

Key Words: Pregnancy, Cancer, Chemotherapy, Outcome, Fetus

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The coexistence of pregnancy and malignancy becomes more common in view of prolongation of reproductive age.[1] Nearly 20% to 30% of malignant tumors are seen in women younger than 45 years.[1] Cancer diagnosed during pregnancy is rare, and incidence of pregnancy-associated all-site cancer is 0.5 to 1.0 per 1000 deliveries or 0.32 to 0.67 per 1000 pregnancies.[2] Therapeutic management of tumor in pregnant women is difficult because of involvement of both mother and fetus.[1] Because of physiological changes in the pregnancy period, diagnosis of malignancy is delayed 5 to 15 months with detection of more advanced stage. For example, breast enlargement due to hormonal changes make it difficult to realize a lump in the breast. And also, melanoma diagnosis may be delayed because of misinterpretation of malignant lesions as hyperpigmentation, which is experienced during gestation.[3] In contrast, pregnancy provides an opportunity for early diagnosis of cervical cancer because visual inspection is routine in antenatal care.[3]

The most common tumors diagnosed during pregnancy are breast cancer, cervical cancer including preinvasive cervical cancer, leukemia, lymphoma, and melanoma, in order of frequency.[1,2,4] Prognosis of the pregnant women with malignancies such as breast cancer and Hodgkin lymphoma (HL) is equivalent to their of nonpregnant counterparts, and termination of pregnancy because of concurrent malignancies does not result in improved prognosis.[4] The effects of chemotherapy (CT) exposure in utero are dependent on gestational age.[3] During the first trimester, in which organogenesis continues, teratogenesis may occur, so CT should not be administered because of increased risk of spontaneous abortions, fetal death, or major malformations.[3] The second and third trimesters are relatively safe when CT is given, although stillbirth, intrauterine growth restriction (IUGR), prematurity, low birth weight (LBW), and fetal myelosuppression may occur at a frequency of 15% to 40%.[1] Because hematologic toxicity can harm both mother and fetus during delivery, 3 to 4 weeks of interval between the last CT and delivery should be waited for.[4] Several reports related whether radiotherapy (RT) can cause harm to the fetus when it was received during gestation,[2,5,6] although it was reported that RT was not contraindicated during pregnancy in specific circumstances with 0.1- to 0.2-Gy threshold dose exposure to the fetus.[6,7] In addition, hormone therapy such as administration of tamoxifen is contraindicated during pregnancy with hormone receptor–positive breast cancer.[8]

Several reports related to CT show that Vinca alkaloids, anthracyclines, 5-fluorouracil (5FU), and cyclophosphamide can be used without much hazards for fetal development, whereas antifolates and alkylating agents are the most detrimental.[1,4] There are large-enough data about anthracycline usage during pregnancy because of its indications both in breast cancer and hematologic malignancies.

In the current study, we report 27 patients with diagnosed malignancy during pregnancy and treated with several modalities during pregnancy or after delivery at 6 medical oncology centers in Turkey.

MATERIALS AND METHODS

This retrospective and descriptive analysis included 27 patients who had been treated during pregnancy or after delivery because of several malignancies in 6 different medical oncology centers in our country between 2001 and 2009. Patients were included if the malignancy was diagnosed during pregnancy. Patient characteristics were recorded including age, gestational age at diagnosis, tumor type, stage, CT type and cycle, and delivery type from the patient's chart. Fetal characteristics including birth weight, congenital anomaly, and prematurity were obtained from the babies' charts. Therapeutic abortion is the termination of a pregnancy to preserve the health of the pregnant female before approximately the 22nd week of gestation. Prematurity is defined as birth before 37 completed weeks of pregnancy. Low birth weight is defined as birth weight of less than 2500 g with more than 37 completed weeks at term. Intrauterine growth restriction is a term used to describe a condition in which the fetus is smaller than expected for the number of weeks of pregnancy. All children were evaluated for any physical, neurological, and hematologic abnormalities from the patient's chart. The states of children were evaluated by taking history from the mothers who were followed up in the oncology department. Treatment and follow-up of all patients were recorded, and all of them were seen every 6 months; a last call was done by one of the authors to update the data of patients who were not seen in the last 3 months.

Statistical Analysis

Data were obtained by using SPSS 15 (SPSS Inc, Chicago, Ill). Median age of the patients was defined. Overall survival was defined as the time between the date of pathological diagnosis and the date of death related to all causes or last known contact. Living patients were censored at the last follow-up visit. Disease-free survival (DFS) was defined as the time from the diagnosis of the malignancy to the recurrence or to the date of death or last known contact.

RESULTS

Several malignancies such as hematologic malignancies, breast cancer, sarcomas, gynecologic malignancies, and others, in order of frequency, were diagnosed in 27 women during pregnancy. Nine of the 27 patients had breast cancers, 11 patients had hematologic malignancy, 2 had gynecologic malignancies, 3 had sarcomas, and others had malignant melanoma and pancreas carcinoma. Whereas chronic myeloid leukemia (CML) and hemangiopericytoma and others were diagnosed in 7 patients during the second trimester, in 2 patients these were diagnosed during the first and third trimesters, respectively. Patients' ages ranged from 22 to 44 years, with a median age of 27 years. Fetal gestational age at diagnosis ranged from 7 to 35 weeks, with a median age of 24.4 weeks. Patient characteristics are shown in Table 1.

Among the 11 hematologic malignancies, the mean age of women, gestational age at diagnosis, and gestational age at the time of CT were 25 years (range, 22–27 years), 25 weeks (range, 7–32 weeks), and 27 weeks (range, 7–32 weeks), respectively. Whereas approximately all of the patients with acute leukemia presented with fatigue, vaginal bleeding, or

TABLE 1. Characteristics of the patients with malignancies diagnosed during pregnancy and treated during gestation or after the delivery

	Malignancy	Maternal Age, y	Stage	Gestation Age During Pregnancy, wk	Gestational Age During CT, wk	CT Type/No. Cycles During Pregnancy	CT Type/No. Cycles After Pregnancy	Maternal Toxicity	Fetal Toxicity	Delivery (Gestational Age Week)	DFS, mo	OS, mo
	Breast cancer											
1	Breast cancer	31	IIIA	31	32	FAC/1	FAC/5	Absent	Absent	C/S (36)	6	11
2	Breast cancer	30	IV	32	32	FEC/3	FEC/3	Absent	Absent	C/S (40)	7	27
3	Breast cancer	29	IIIA	33	34	AC/2	AC/2-T/4	Absent	Absent	C/S (39)	11	12
4	Breast cancer	43	IIA	16	16	None	Tamoxifen	Absent	Therapeutic abortion	Therapeutic abortion	24	26
5	Breast cancer	26	IIIC	22	24	AC/4	T/4	Gastrointestinal grade 2	Absent	N (35)	30	29
6	Breast cancer	31	IIB	29	None	None	Op-FEC(6)-RT	Absent	Absent	N (39)	74	96
7	Breast cancer	35	IIB	35	None	None	Op-FEC(3)-T(3)-RT	Absent	Absent	C/S (38)	17	23
8	Breast cancer	38	IV	7 (Bone metastasis)	None	None	RT-tamoxifen	Absent	Absent	C/S (37)	118	120
9	Breast cancer	41	IIA	21	None	None	Op-FEC(6)-RT	Prematurity	Eclampsia	C/S (33)	44	47
	Hematologic malignancy											
10	AML	24		26	27	Ara-daunorubicin/2	Ara-daunorubicin/4	Absent	prematurity	C/S (30)	4	18
11	AML	25		21	21	Ara-daunorubicin/4	Ara-daunorubicin/2	Absent	Absent	C/S (37)	24	24
12	ALL	27		25	26	Steroid + vincristine/3	Steroid + vincristine/3	Absent	Absent	C/S (37)	37	37
13	CML	25		24	25	Hydroxyurea/3	Hydroxyurea/3	Absent	Absent	N (37)	44	55
14	CML	25		7	7	None	imatinib	Absent	Therapeutic abortion	Therapeutic abortion	48	48
15	HL	25	IIA	24	24	ABVD/3	ABVD/3	Absent	Absent	C/S (36)	41	36
16	HL	23	IIA	27	27	ABVD/2	ABVD/4	Absent	IUGR	N (35)	4	4
17	NHL	22	III	28	29	CHOP/2	CHOP/4	Absent	Absent	N (35)	6	7
18	NHL	23	IIB	27	29	R-CHOP/2	R-CHOP/4	Absent	Absent	N (35)	2	2
19	NHL	24	IIB	32	32	CHOP/3	CHOP/3	Absent	Absent	N (40)	3	2
20	NHL	25	IIIB	25	27	R-CHOP/2	R-CHOP/4	Absent	Absent	N (35)	27	27
	Gynecologic malignancy											
21	Ovarian cancer	28	II	40	None	None	BEP/3	Absent	Absent	N (41)	2	3
22	Cervix cancer	35	IB2	22	22	None	Cisplatin-RT	nephrotoxicity	Therapeutic abortion	Therapeutic abortion	18	26
	Soft-tissue tumors											
23	Ewing sarcoma	30	II	30	None	None	Op-IE-VAC (8)	Absent	Absent	N (36)	9	9
24	Soft-tissue sarcoma	23	IV	32	32	CVADIC/1	CVADIC/4	Absent	Prematurity, LBW	C/S (33)	48	3
25	Hemangiopericytoma	30	I	14	14	RT	None	Absent	Therapeutic abortion	Therapeutic abortion	14	46
	Others											
26	Pancreas cancer	44	IV	30	31	Cisp-5FU/1	Cisp-5FU/2	Nephrotoxicity	Prematurity, LBW	N (33)	2	2
27	Malignant melanoma	27	IV	27	28	IFN/2	IFN/2	Absent	Absent	C/S (36)	11	12

ALL, acute lymphoid leukemia; IFN, interferon; N, normal vaginal delivery; Op, operation; IE-VAC, ifosfamide, etoposide–vincristine, doxorubicin, cyclophosphamide.

epistaxis, patients with malignant lymphoma mostly complained of B symptoms such as sweating, weight loss, or fever. All of the patients with hematologic malignances were treated during gestation. CML in one of the patients was diagnosed during the seventh week of gestation, and she underwent therapeutic abortion, then imatinib therapy was given; CML in the other patient was diagnosed at 24 weeks of gestation, and hydroxyurea was given for 3 cycles without any fetal complication. Patients with HL were treated with a median of 2 cycles (range, 2–3 cycles) of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and R-CHOP (rituximab, CHOP) with a median of 2 cycles (range, 2–3 cycles) was given to 4 patients with non-Hodgkin lymphoma (NHL). Treatment was continued after the delivery with CT and RT for stage II patients and with CT only for stage III patients. Ara-C (cytosine-arabinoside) CT was administered to 2 of the patients with acute myeloid leukemia (AML) during the second and third trimesters of pregnancy, and 1 patient with acute lymphoid leukemia was treated with steroid and vincristine for 3 cycles at the third trimester. Both median DFS and overall survival (OS) times of the patients were 24 months (range, 2–48 months for DFS, 2–55 months for OS).

Totally, 9 patients with breast cancer presented with breast mass during pregnancy and diagnosed using Tru-cut biopsy, and 7 of them underwent mastectomy and axillary lymph node dissection, but the remaining 2 patients were not able to undergo operation because of stage IV disease. The mean age of women, gestational age at the diagnosis, and gestational age at the time of CT were 31 years (range, 26–43 years), 29 weeks (range, 7–35 weeks), and 32 weeks (range, 16–34 weeks), respectively. Mastectomy and axillary lymph node dissection were performed during pregnancy in 4 patients with breast cancer, but in 3 of them, these were carried out after delivery. The patients had locally advanced disease with axillary lymph node metastasis (4 of them were stage II, 2 of them were stage III, and others were stage IV disease). Of 4 patients who received CT during the second and third trimesters of pregnancy, one of the patients preferred therapeutic abortion when she had a breast cancer at 16 weeks of gestation. Seven of the breast cancer patients were treated with RT because of axillary lymph node involvement after the delivery. All the breast cancer patients were given anthracycline-based CT including FAC/FEC (5FU, adriamycin/epirubicin, cyclophosphamide) or AC (adriamycin, cyclophosphamide) during or after the delivery. Four patients received CT during the third trimester, 3 patients received CT after the delivery, and the other one with bone metastasis was treated with tamoxifen and RT without CT. Only 1 prematurity was seen because of eclampsia of the mother during FEC regimen, so cesarean delivery (C/S) was performed. The median DFS and OS intervals of women with breast cancer diagnosed during their pregnancies were 24 months (range, 6–118 months) and 27 months (range, 11–120 months), respectively.

Sarcomas, as like hemangiopericytoma, originated from the right leg; Ewing sarcoma of the pelvis; and soft-tissue sarcoma located in the retroperitoneal region were diagnosed in 3 patients. The patient with hemangiopericytoma underwent therapeutic abortion because the diagnosis was made at 14 weeks, then RT was applied. Ewing sarcoma in 1 patient was diagnosed during the 30th week of gestation, and CT-RT and operation were delayed after the end of delivery, with mother's and surgeons' decision. Although the patient with soft-tissue sarcoma had the diagnosis at the 23rd week of gestation, CT could be given at the 32nd week of gestation, and CVADIC (doxorubicin, cyclophosphamide, vincristine, dacarbazine) regimen was continued after the delivery. One of the patients was diagnosed as having gynecologic malignancy, which was cervical cancer, who underwent therapeutic abortion; because the diagnosis was made at 22 weeks of gestation, the prognosis was poor. After the therapeutic abortion, the patient received RT combined with cisplatin, and maternal nephrotoxicity was seen. In the other patient, stage II ovarian germ cell tumor (dysgerminoma) was diagnosed at the 40th week of gestation, and delivery was waited before giving BEP (bleomycin, etoposide, cisplatin) regimen.

The remaining 2 patients had pancreas cancer and malignant melanoma, and both malignancies were diagnosed during the third trimester; these patients received CT and immunotherapy (interferon), respectively, during gestation.

There were not any congenital malformations and perinatal death in the fetus due to exposure to CT, and also, no any stillbirths or miscarriages occurred in patients who received FAC, CHOP, R-CHOP, Ara-C, and hydroxyurea during the second or third trimester. The majority of patients delivered their infant at term. Only 3 fetuses were delivered prematurely, who were treated with cisplatin-5FU, CVADIC, and Ara-C during the intrauterine period because of maternal pancreas carcinoma, soft-tissue sarcoma, and acute leukemia, respectively. None of the fetuses had any significant neonatal complications. Two patients with pancreas cancer and soft-tissue sarcoma had babies with LBW. The median birth weight of babies exposed to CT during gestation was 3300 g (range, 2850–3500 g). No neonatal cytopenia was reported due to delivery that occurred more than 3 weeks after the last CT was given to the mother. None of the patients were allowed for lactation. In our study, good perinatal outcomes of the fetus may be related to both cancer type and stage and the treatment.

The median follow-up duration was 19.7 months (range, 2–122 months). Although perinatal outcomes of our patients were defined clearly, information about the long-term outcomes of the children was not clear, dependent on patients' expression.

DISCUSSION

The most common tumor diagnosed during pregnancy is breast cancer, and surgery can be performed during pregnancy or after delivery, depending on the time of diagnosis.[2] Breast cancer surgery during pregnancy had been shown to be safe in 18 patients with pregnancy-associated breast cancer (PABC).[9] Radiotherapy is contraindicated during pregnancy, so mastectomy may be more preferred than breast conservation surgery.[2,5] Although Kal and Struikmans[6] reported that pregnancy was not contraindicated to RT in patients with breast cancer, they also reported that irradiation of maternal breast or chest wall exposes the fetus to 0.05 to 0.15 Gy,

which is within the threshold dose that can cause fetal malformation. In our series, 7 patients with breast cancer underwent mastectomy and axillary lymph node dissection. One of the patients decided therapeutic abortion because of diagnosis at the 16th week of gestation. Operations were performed after delivery in 3 patients with breast cancer. In the literature, it is recommended that CT should not be delayed unless the patient is within the 2 to 3 weeks of delivery (around 37 weeks of gestation).[5] In 2 of our patients, breast cancer was diagnosed at the end of the third trimester (29 and 35 weeks), and they decided, together with their family, delaying the treatment until after the delivery. Although the other patient had the diagnosis at 21 weeks of gestation, pregnancy was ended prematurely because of eclampsia, then CT and RT followed mastectomy. Berry et al[9] reported 24 patients with PABC treated with FAC during the second and third trimesters of pregnancy without any fetal malformation. Ring et al[10] also reported 15 breast cancer patients treated with anthracycline-based regimens during gestation, with 1 IUGR and 2 unspecified respiratory problems. García-Manero et al[11] reported 11 patients with PABC treated with anthracycline-based CT. Four of them were also given taxanes, without any fetal malformations. In our series, anthracycline-based CT regimens were given to 4 PABCs at the second and third trimesters without any complication for the mother or babies. In an MD Anderson Cancer Center large prospective series including 57 patients with localized breast cancer and treated with FAC regimen, the authors did not report any stillbirths, miscarriages, or perinatal death. The median gestational age at CT initiation, median gestational age at delivery, and birth weight were 23 weeks, 37 weeks, and 2890 g, respectively.[7] In our series, the median gestational age at the beginning of the CT was 24.4 weeks, similar to that in literature.

In the review of 50 cases, 48 with breast cancer, 1 with NHL, and the other one with AL, epirubicin-based CT was given in 47 patients during the second and third trimesters of pregnancy. One intrauterine death at the 3rd week, 1 stillbirth, and 1 neonatal death at day 8 were seen. In 2 cases, epirubicin administered at the first trimester led to spontaneous abortion.[12] None of our patients received anthracycline-based CT during the first trimester, and no any stillbirths or neonatal mortality was seen. Anthracycline-based CT was given to 10 of our patients because of HL and NHL and breast cancer at the second and third trimesters.

Tamoxifen is contraindicated during pregnancy.[8] In 1 of our patients with breast cancer that was diagnosed at 16 weeks of pregnancy, tamoxifen was given followed by therapeutic abortion, which was the preference of the patient to avoid risk of delaying treatment. Although termination of pregnancy does not improve survival for breast cancer patients,[2] 1 of the 9 breast cancer patients preferred therapeutic abortion in our study.

In our series, cervical cancer in 1 patient with was diagnosed at the 21st week of gestation. Because of positive pelvic lymph nodes and stage IIIB, which were the most important prognostic factors in early-stage cervical cancer, standard therapy such as postoperative cisplatin and brachytherapy were applied, followed by abortion. Although it is recommended that therapeutic abortion should be offered when the diagnosis of cervical cancer was made before the 20th week of gestation,[4] our patient underwent therapeutic abortion at the 21st week of gestation because of poor prognostic factors.

When lymphoma is diagnosed during the first trimester, treatment with standard CT after pregnancy termination is recommended.[13] Treatment of stage I HL or indolent NHL can be delayed until the end of the first trimester.[13] Hodgkin lymphoma is the most common type of lymphoma during pregnancy.[13] The decision of CT during pregnancy should be weighed against the effect of treatment delay on maternal survival. Single-agent CT with anthracyclines or Vinca alkaloids followed by standard ABVD regimen at the end of the first trimester can be considered as safe for HL.[13] Although there are insufficient data about using CHOP CT at the first trimester of pregnancy, existing data suggest that CHOP can be safely used in the treatment of pregnant women with NHL at the second and third trimesters, without adverse fetal outcomes.[13] Rituximab may be considered as reliable when it is combined with CHOP for the treatment of $CD20^+$ diffuse large B-cell lymphoma during pregnancy.[14] All of our 4 NHL patients were successfully treated with CHOP and R-CHOP at the third trimester without any fetal morbidity. Two patients with HL were also treated with standard ABVD regimen without fetal morbidity, except for 1 fetus with IUGR.

The association between AL and pregnancy is rare, and more than two thirds of ALs that were diagnosed during pregnancy is AML.[14] Maternal prognosis is adversely affected if treatment is delayed.[14] Therapeutic abortion is recommended for patients with AL diagnosed during the first trimester.[14] One review showed that cytarabine and anthracyclines were not associated with teratogenicity when they were given at the first trimester due to AL.[15] Chelghoum et al[14] reported 37 patients with AL diagnosed during pregnancy, and whereas 15 pregnancies were ended with therapeutic or spontaneous abortion, 15 healthy fetuses exposed to CT in utero and 7 premature deliveries were seen. Herein, 3 of the 5 patients with hematologic malignancy had AL; the others had CML, and they were treated with Ara-C, corticosteroid-vincristine, and hydroxyurea during pregnancy, respectively. There was 1 patient with AML treated with Ara-C during the 27th week of gestation that ended prematurely. In the literature, there were 23 cases with CML treated with imatinib during pregnancy.[16] Pregnancy was terminated prematurely in 5 of them; imatinib was discontinued in 13 cases at the fourth to ninth week of gestation. In our series, 1 patient with CML was treated with imatinib followed by therapeutic abortion at the seventh week of gestation because of limited experiences related to imatinib usage during pregnancy.

Van Calsteren et al[17] reported 9 pregnant women treated with CT for different malignancies between the 15th and 37th week of gestation. Eight children were born before the 37th week, and 3 babies were born with LBW. Low birth weight is reported in up to 40% of cases as a result of IUGR or premature labor.[18] In our series, we detected 2 fetuses who were exposed CT in utero delivered with LBW because of premature labor. Induction of labor is not recommended before 32nd to 34th week of gestation, unless the mother

refuses the CT during gestation or CT extension is necessary until the last month of gestation.[18] At the first trimester, CT causes 10% to 20% risk of major malformations.[3] A study including 210 cases demonstrated that 27 of 29 fetal abnormalities were associated with first-trimester exposure.[10] After the first trimester, CT does not increase the risk of malformation except for preterm delivery, small for gestational age, IUGR, infant leukopenia, and tachycardia.[10] A review that included 376 fetuses exposed to CT after organogenesis reported that 6% neonatal or fetal deaths, 7% IUGR, 5% premature delivery, and 4% myelosupression.[10] None of our patients were treated with CT during the first trimester.

Possible pregnancy outcomes for pregnancy-associated cancer include normal vaginal delivery, preterm deliveries, C/S, stillborn, and therapeutic abortions.[2] Several studies showed that the birth weights of babies were similar whether the mothers were treated with CT during pregnancy or not.[18] The median birth weight of babies was 3300 g in the present study. Although in the past the incidence of prematurity was higher because of limited CT exposure of fetus by elective C/S, it is usually recommended that pregnancy should go to the term.[5] Three pregnancies were ended prematurely, which were cases of advanced-stage pancreas cancer, soft-tissue sarcoma, and AML, in our study. Chemotherapy was interrupted in all of our patients 3 weeks before delivery to avoid fetal and maternal leukopenia and sepsis, as compatible with the literature.

In conclusion, pregnancy-related cancers are relatively rare, so there are no standard guidelines related to their management. Chemotherapy may be reliable after the first trimester, and it is generally well tolerated. Long-term effects of CT could not be sufficiently understood, and they require additional investigations. Therefore, prospective randomized controlled studies associated with not only the treatment of cancer during pregnancy but also the impacts of CT on the mother and the fetus are needed.

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