Cancer and pregnancy: what should we know about the management with systemic treatment of pregnant women with cancer?

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Abstract

The incidence of cancer during pregnancy is a rare phenomenon and is estimated to occur in 1:1000 pregnancies. This co-existence is likely to rise since the delay of childbearing to the later reproductive age is nowadays more common in families. The most frequent malignancies diagnosed during pregnancy are breast cancer, cervical cancer, haematological malignancies (lymphomas and acute leukaemias) and melanoma. Less common tumours are gastrointestinal, urological and lung cancers [1].

Principles of systemic treatment

In all cases a multidisciplinary therapeutic approach among obstetrician, gynaecologist, surgical oncologists, radiation oncologists, medical oncologists and haematologists is required.

The administration of systemic treatment in these patients should follow certain important rules such as:

(a) medical oncologists should treat the pregnant mother and should protect the fetus
(b) no chemotherapy is allowed during the period of organogenesis (first trimester)
(c) chemotherapy should only be administered during the second and third trimesters
(d) endocrine treatment should be avoided
(e) tyrosine-kinase inhibitor and monoclonal antibodies should not be administered owing to insufficient evidence [1,2].

Safety of chemotherapy drugs in pregnancy

The adverse effects of systemic cancer treatment on the mother, the fetus or the neonate are either immediate or delayed. Spontaneous abortion, teratogenesis, organ toxicity, premature birth or low birth weight, are characterised as immediate effects, whereas carcinogenesis, retarded physical or mental development and sterility in the mother are delayed effects.

Of 826 pregnant women with cancer treated with chemotherapy for various types of cancer up to 2008, 92 fetal malformations (11%) were recorded (Table 1). The following malformations were listed: (a) *chromosomal syndromes* (Down syndrome, group C trisomy mosaicism), (b) *neurological disorders* (hydrocephalus, brachycephaly, sensorineural hearing loss, hypoplasia of the anterior cranial base and midface, macrognathia, cleft palate), (c) *skeletal disorders* (clubfoot, absent big toes, short limbs and digits, syndactyly, cranial dysostosis, bilateral four-fingered hands, absent radii, delayed ossification), (d) *ocular disorders* (adherence of the iris), (e) *cardiac defects* (single left coronary artery, bicuspid aortic valve, ventriculomegaly, myocardial necrosis, dilated cardiomyopathy), (f) *urogenital defects* (bilateral ureteral reflex, unilateral or bilateral renal agenesis, ambiguous genitalia, IUGR), (g) *GI disorders* (imperforated anus, oesophageal atresia, pyloric stenosis and finally premature delivery, miscarriages, spontaneous abortions) [3].

Table 1
Chemotherapy and fetal malformations

Chemotherapy Group	Number of pregnant women treated	Number of fetal malformations (%)
Alkylating agents	193	21 (11%)
Antimetabolites	233	41 (17.5%)
Antibiotic agents	294	24 (8%)
Antimitotic agents	106	6 (5.5%)
Total	**826**	**92 (11%)**

Systemic chemotherapy by tumour type

Breast cancer

Chemotherapy

In total, 156 pregnant patients with breast cancer were treated with chemotherapy on neoadjuvant or adjuvant

Table 2
Chemotherapy in pregnant mothers with breast cancer

Setting	Number	Regimen	Gestational trimester	Reported complications/malformations	
				Mother	Fetus
Neoadjuvant/adjuvant	120	Anthracycline-based	< 2nd: 1/120	Unintentional pregnancy (1 reported)	Bicuspid aortic value High arched palate Syndactyly
			> 2nd: 119/120	none	none
	6	Anthracycline/taxane-based	> 2nd: 6/6	none	none
	28	CMF	< 2nd: 3/28	Spontaneous abortion (1 reported)	Intrauterine death Mental retardation Poor physical development
			> 2nd: 25/28	none	none
	2	5-FU/Vinorelbine	> 2nd: 2/2	none	none
Metastatic disease	13	Anthracycline-based	> 2nd: 13/13	none	none

CMF: cytoxan, methotrexate, fluorouracil; 5-FU: 5-fluorouracil.

setting up to 2009 [4]. Only two studies with 77 patients were prospective. One hundred and twenty-six patients received anthracycline-based chemotherapy and the rest non-anthracycline-containing regimens, mainly CMF. Almost 98% of them were treated after the second gestational trimester. Only two mothers experienced pregnancy complications, one with unintentional pregnancy and one with spontaneous abortion. Fetal malformations were observed in 3.2% of patients treated during the first trimester. Bicuspid aortic valve, high arched palate, syndactyly, mental retardation, poor physical development, Down syndrome, clubfoot or congenital bilateral ureteral reflux were observed in five fetuses.

Thirteen patients with metastatic breast cancer were treated with anthracycline-based chemotherapy after the second trimester of pregnancy. In neither mothers nor fetuses were complications or malformations recorded (Table 2).

HER2/neu targeted agents

Thirteen patients were exposed to trastuzumab and one to lapatinib [4]. Eight had trastuzumab monotherapy, three trastuzumab with chemotherapy and two with endocrine therapy. Concerning pregnancy complications, four experienced anhydramnios, three oligohydramnios, one ectopic pregnancy, one preterm premature rupture of membranes, one fetal intrauterine growth restriction and one vaginal bleeding. Respiratory failure or renal failure was observed in five and four fetuses respectively. There were also four fetal deaths.

Endocrine treatment

A review of Astra Zeneca files noted 50 individuals who were treated with tamoxifen during gestation, with ten congenital defects recorded [4]. In another chemoprevention study with tamoxifen, 85 pregnancies were reported without any fetal complications (Table 3).

Gynaecological cancers

Cervical cancer

In total, 23 pregnant patients with squamous cell cervical carcinoma were traced [4]. All of them were treated during the second and third trimester. Almost half of these patients were treated with cisplatin as a single agent, while the other half were treated with cisplatin-based chemotherapy with or without radiation therapy. In the majority of patients the gestational delivery age was below 34 weeks. Pregnancy outcome was normal in all patients, whereas fetal outcome was normal in 77%. Four intrauterine fetal deaths and one case of renal failure were observed (Table 4).

Ovarian cancer

Thirty-eight ovarian cancers (20 epithelial and 18 non-epithelial), treated with systemic chemotherapy, mostly cisplatin combinations, were reported [4]. All patients were managed after the second gestational trimester. Normal pregnancy and fetal outcome was noted in 80–83% and 89–95% respectively. Concerning fetal malformation respiratory failure, ventriculomegaly and fetal deaths were found. Rarely, hypertension, oligohydramnios, intrauterine growth

Table 3
Other systemic treatment in pregnant mothers with breast cancer[a]

Setting	Number	Drugs	Gestational trimester	Complications/malformations	
				Mother	Fetus
Hormonal treatment					
Adjuvant	53	Tamoxifen	> 2nd	none	Ambiguous genitalia Goldenhar syndrome Other congenital defects (10)
Chemoprevention	85	Tamoxifen	–	none	none
HER/new targets agents					
Adjuvant	6	Trastuzumab ± Hormonal Rx (2)	<2nd	Anhydramnios (4) Oligohydramnios (3)	Respiratory failure (5) Renal failure (3)
Metastatic	7	Trastuzumab ± Chemotherapy (3)	<2nd	Ectopic pregnancy (1) PROM (1) IUGR (1) Vaginal bleeding (1)	Fetal deaths (4)
Metastatic	1	Lapatinib	< 2nd	none	none
Anti-osteoporotic treatment in pregnant non-cancer mothers	72	Bisphosphonates	<2nd	none	none

[a] Numbers reported are shown in parentheses.

Table 4
Chemotherapy in gynaecological cancers during pregnancy

	Cervical cancer	Epithelial ovarian cancer	Non-epithelial ovarian cancer
Number of patients	23	20	18
Pathology	Squamous carcinoma	65% serous carcinoma	Endodermal sinus 55.5% Germ cell 33.5% Others 11%
Chemotherapy	Cisplatin only: 48% Cisplatin-based: 30.5% Cisplatin + RT: 21.5%	Platinum alone: 35% Platinum-based: 40% Taxane ± platinum: 25%	BEP/EP/PVB 72% Others 28%
Trimester	>2nd (all patients)	>2nd (all patients)	>2nd (all patients)
Gestational age at delivery	< W34: 74% > W34: 21.5% Abortion: 4.5%	< W34: 20% > W34: 80%	< W34: 17% > W34: 83%
Fetal outcome	Normal: 77% IUFD: 18% ↑ Creatinine: 4.5%	Normal: 95% Fetal death: 5%	Normal: 89% Respiratory failure/anaemia: 5.5% Ventriculomegaly: 5.5%
Pregnancy outcome	–	Normal: 80%	Normal: 83%

Table 5
Other solid tumours treated with chemotherapy

Tumour type	Number of patients	Chemotherapy	Trimester	Complications	
				Maternal	Fetal
Sarcomas	13	Doxorubicin-based: 10 Non-doxorubicin-based: 3	< 2nd: 15% > 2nd: 85%	16%	23%
Lung Cancer	8	Cisplatin-based: 8 Erlotinib: 1	< 2nd: 25% > 2nd: 75%	none	Transient fetal respiratory distress (38%) due to prematurity
Melanoma	4	Cisplatin-based	-	none	25%
Colorectal	2	FOLFOX-6	> 2nd: 100%	none	none

Table 6
Chemotherapy in Hodgkin's and non-Hodgkin's lymphoma during pregnancy

	Hodgkin's lymphoma	Non-Hodgkin's lymphoma
Number of patients	42	46
Chemotherapy		
ABVD/ABV	45%	CHOP 33%
MOPP	10%	Other anthracycline-based 33%
Other	45%	Other 34%
Trimester		
<2nd	40.5%	20%
>2nd	59.5%	80%
Fetal outcome		
Normal	76%	83%
Malformations	24% (3 died)	17% (1 died)
Pregnancy outcome		
Normal	93%	96%
Spontaneous abortion	7%	4%

restriction, preeclampsia or premature membrane rupture were observed (Table 4).

Other solid tumours

Very few cases of patients with other solid tumours treated with chemotherapy have been published, including sarcomas, lung cancer, melanoma, colorectal cancer, head and neck cancer or brain tumours (Table 5) [4].

Lymphomas

Forty-two pregnant women with Hodgkin's lymphoma and 46 with mainly diffuse large B-cell non-Hodgkin's lymphomas managed mostly with anthracycline-based chemotherapy were detected in the English-language literature [5]. Sixty and 80% of these patients were treated after the second or third trimester respectively. Normal pregnancy outcome was found in 93% of Hodgkin's lymphoma (HL) and in 96% of the non-Hodgkin's lymphoma (NHL) patients, while 4–7% of them had spontaneous abortions. In addition, fetal outcome was normal in 76% and 83% respectively. Twenty-four percent of fetuses, of the HL group and 17% of the NHL group had malformations, with four post-natal fetal deaths. Most fetal adverse events are noticed when lymphomas are diagnosed during the first trimester. Therefore, in these particular cases pregnancy termination is indicated, especially if waiting until the second trimester is not feasible.

Rituximab data are available in seven cases. All patients had an unremarkable pregnancy course; however, three neonates had undetectable or decreased CD19+ B cells, which was reversible within 3–6 months (Table 6).

Radiotherapy to localised disease with cervical or axillary lymphadenopathy has been advocated, although it is not generally accepted.

Leukaemias

Chronic myelogenous leukaemia

During the pre-imatinib era, 49 patients treated with hydroxyurea and five with busulfan were identified [5]. Although the majority of these patients had chemotherapy during the first trimester, very few congenital anomalies have been reported. Similar results were obtained from 26 chronic myelogenous leukaemia (CML) patients exposed to interferon-alpha.

In total, 36 patients were managed with imatinib and 64% were treated during the first gestational trimester. Normal pregnancy outcome was noticed in 95% of the cases and normal fetal outcome in 89%. Two hypospadias, one pyloric stenosis and one meningocele were observed.

Acute myelogenous leukaemia

Eighty-seven cases of acute myelogenous leukaemia (AML) during pregnancy were identified, 64 treated with chemotherapy during the second and third trimesters [5]. The most common drugs used were cytarabine and daunorubicin. Almost half of the patients treated during the first trimester had poor fetal outcome. Even patients treated after the first trimester experienced a high incidence of maternal or fetal complications mostly attributed to daunorubicin and idarubicin.

Acute lymphoblastic leukaemia

Twenty-one patients with acute lymphoblastic leukaemia (ALL) exposed to chemotherapy following the first trimester were traced [5]. Most cases were treated with daunorubicin or idarubicin-based chemotherapy. A high incidence of fetal complications was observed.

Acute promyelocytic leukaemia

Twenty-two cases of acute promyelocytic (APL) treated with all trans-retinoic acid with or without chemotherapy [5]. Maternal or fetal adverse events were noticed again in mothers or newborns treated with daunorubicin or idarubicin chemotherapy.

Conflict of interest statement

The author declares not any conflict of interest.

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