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Cancer During Pregnancy: An Analysis of 215 Patients Emphasizing the Obstetrical and the Neonatal Outcomes

Kristel Van Calsteren, Liesbeth Heyns, Frank De Smet, Liesbet Van Eycken, Mina Mhallem Gziri, Willemijn Van Gemert, Michael Halaska, Ignace Vergote, Nelleke Ottevanger, and Frédéric Amant

ABSTRACT

Purpose

The aim of this study was to assess the management and the obstetrical and neonatal outcomes of pregnancies complicated by cancer.

Patients and Methods

In an international collaborative setting, patients with invasive cancer diagnosed during pregnancy between 1998 and 2008 were identified. Clinical data regarding the cancer diagnosis and treatment and the obstetric and neonatal outcomes were collected and analyzed.

Results

Of 215 patients, five (2.3%) had a pregnancy that ended in a spontaneous miscarriage and 30 (14.0%) pregnancies were interrupted. Treatment was initiated during pregnancy in 122 (56.7%) patients and postpartum in 58 (27.0%) patients. The most frequently encountered cancer types were breast cancer (46%), hematologic malignancies (18%), and dermatologic malignancies (10%). The mean gestational age at delivery was 36.3 ± 2.9 weeks. Delivery was induced in 71.7% of pregnancies, and 54.2% of children were born preterm. In the group of patients prenatally exposed to cytotoxic treatment, the prevalence of preterm labor was increased (11.8%; $P = .012$). Furthermore, in this group a higher proportion of small-for-gestational-age children (birth weight below 10th percentile) was observed (24.2%; $P = .001$). Of all neonates, 51.2% were admitted to a neonatal intensive care unit, mainly (85.2%) because of prematurity. There was no increased incidence of congenital malformations.

Conclusion

Pregnant cancer patients should be treated in a multidisciplinary setting with access to maternal and neonatal intensive care units. Prevention of iatrogenic prematurity appears to be an important part of the treatment strategy.

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INTRODUCTION

Cancer treatment during pregnancy is a challenge. Although surgery has been shown to be safe during pregnancy,^{1,2} only a few drugs have been tested in pregnant women. Hence, most drugs are classified as “contraindicated during pregnancy, unless strictly needed.”³ Therefore, physicians must assess whether the benefits of treatment for the mother outweigh the potential risk to the fetus.

Chemotherapy and radiotherapy were long considered incompatible with normal fetal development. This policy resulted in either termination of pregnancy or suboptimal cancer treatment for the mother. Clinicians have gained some experience in this field from case reports and small studies. In contrast to previous assumptions, the short-term outcome after prenatal exposure to chemotherapy or radiotherapy initiated after the first gestational

trimester appears to be positive.⁴⁻⁷ Studies on the long-term outcome of prenatal exposure to chemotherapy show a reassuring outcome for the children.^{8,9} However, because the described or applied methodology in these studies was rather poor, additional research is necessary.

The concurrence of cancer and pregnancy is a relatively rare problem, occurring in about one in 1,000 pregnancies.¹⁰ Therefore, single institutional or regional initiatives will not be able to provide sufficient information on the safety of cancer treatment during pregnancy for both the mother and fetus. Since more women are delaying childbearing and the incidence of cancer in the 30 to 49 years age group is increasing, it can be expected that in the future, cancer will be diagnosed more often in pregnant women.^{11,12} To gain more data and obtain better counseling for the patient, the need for a multicenter registration is growing.¹³ Therefore, we

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initiated an international collaborative study investigating the problem of cancer during pregnancy. In this study, we focus on management options and the impact on the obstetric and neonatal outcomes.

PATIENTS AND METHODS

In an international collaborative setting, patients with invasive cancer diagnosed during pregnancy were identified. Patients with a preinvasive disease were excluded. To ensure uniformity in obstetric and oncologic management, patients diagnosed before 1998 were excluded in the current analyses. The study was approved by the institutional review board in the University Hospitals of Leuven, Belgium; Nijmegen, the Netherlands; and Prague, Czech Republic.

Because information on pregnant state is not available in most cancer registries and because oncologic problems are not registered in perinatal data sets, we attempted to contact as many physicians who treat pregnant cancer patients as possible by means of networking (eg, mailing members of the Flemish Society of Obstetrics and Gynecology); newsletters; presentations at congresses for obstetricians, hematologists, or oncologists; and a Web site (www.cancerinpregnancy.org). We asked physicians to register the patients they treat or had treated and to trace patients by means of their institutional data sets and hospital registration systems.

In Belgium, a collaboration was established with the Foundation Cancer Registry and one medical insurance organization (National Alliance of Christian Sickness Funds). Registration codes for chemotherapy and radiotherapy were linked to the code for delivery or in utero death (> 16 weeks of gestation) with a maximum time interval of 9 months between both. The list of patients we obtained was fine-tuned in such a way that only the patients with a cancer diagnosis during pregnancy remained. Treating physicians of these patients were contacted by the Foundation Cancer Registry with a request to register their patients anonymously in this study.

Clinical data were collected and analyzed in accordance with local privacy legislation. Oncologic, obstetric, and pediatric files were screened to retrieve clinical information. Oncologic data included the type of cancer, the date of diagnosis, and the type and date of treatment. Obstetric data we attempted to retrieve included gestational age at diagnosis, obstetric complications, gestational age at delivery, and mode of delivery (induction, cesarean

section, spontaneous labor). Pediatric data collected included birth weight, sex, congenital malformations, admission to neonatal intensive care unit (NICU), and reason for admission.

All data were collected in a Microsoft Access database and processed in Microsoft Excel 2007 (Microsoft, Redmond, WA). Unless mentioned otherwise, values are reported as mean ± standard deviation. Statistical testing was performed with Graphpad Prism 5 and its online software (<http://www.graphpad.com/quickcalcs/index.cfm>). Two-sided tests were applied. The Wilcoxon rank sum test was used for comparing continuous variables in two groups; for more than two groups, the Kruskal-Wallis exact test was used. A binomial exact test was used for comparing a proportion with an expected value. Results were considered significant at $P < .05$.

RESULTS

Between 1998 and 2008, 215 patients with a diagnosis of cancer during pregnancy were registered. The distribution by country was 147 (68.4%) in Belgium, 55 (25.6%) in the Netherlands, and 13 (6.0%) in the Czech Republic. The maternal age at diagnosis was 33.2 ± 4.8 years and the gestational age was 21.0 ± 10.8 weeks. The timing of cancer diagnosis in pregnancy was distributed as follows: 52 (24.2%) in the

Tumor Type	No.	%
Breast cancer	99	46
Hematologic malignancies	40	18
Hodgkin's disease	13	6.0
Non-Hodgkin's lymphoma	10	4.7
Acute lymphatic leukemia	4	1.9
Acute myelogenous leukemia	7	3.2
Chronic myelogenous leukemia	4	1.9
Hairy cell leukemia	1	0.5
Multiple myeloma	1	0.5
Dermatologic malignancies	21	10
Basal cell carcinoma	9	4.2
Melanoma	11	5.1
Kaposi's sarcoma	1	0.5
Cervical cancer	17	8
Brain tumor	8	4
Ovarian cancer	8	4
Colorectal cancer	5	2
Other (sarcoma, lung, liver, kidney, GI stromal tumor, thyroid, urachus, rhinopharyngeal)	17	8
Total	215	100

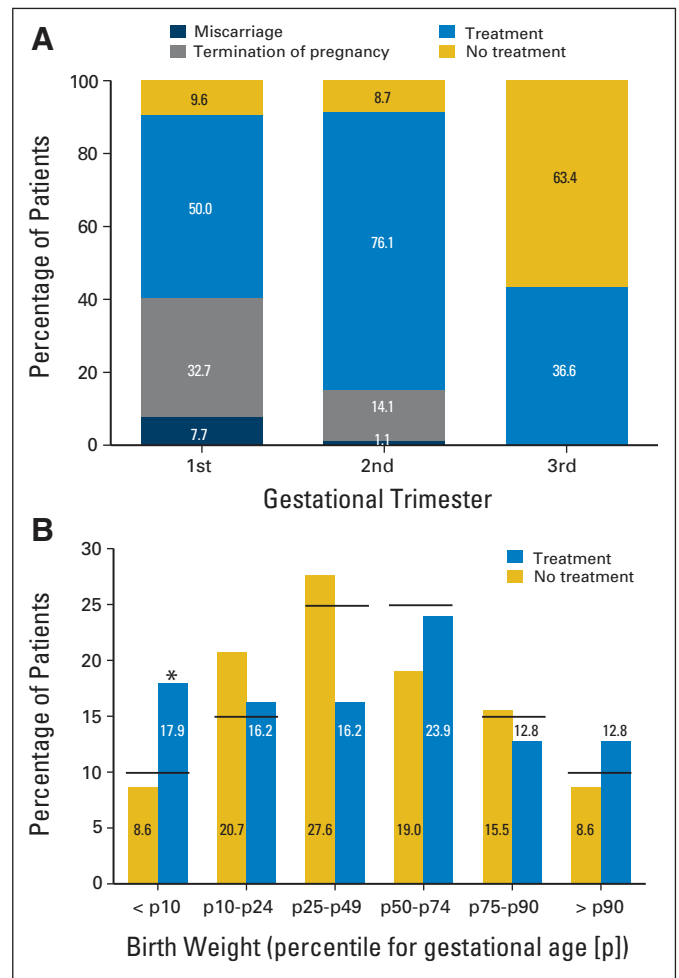


Fig 1. (A) Management of cancer during pregnancy per trimester (n = 215). (B) Distribution of birth weight (n = 175) expressed in percentile for gestational age (p) (* $P = .012$).

first trimester, 92 (42.8%) in the second trimester, and 71 (33.0%) in the third trimester.

Oncologic Problems

The distribution of cancer types is depicted in Table 1. The most frequently encountered tumor types were breast cancer (46%), hematologic malignancies (18%), and dermatologic malignancies (10%). Primary and recurrent cancer were diagnosed in 204 and 11 patients, respectively.

Treatment Policy Related to Pregnancy

In five (2.3%) of 215 patients, a miscarriage occurred at 10.7 ± 4.8 weeks of gestation, before cancer treatment was started. In 30 (14.0%) of 215 patients, the pregnancy was terminated at a gestational age of 10.9 ± 6.8 weeks. In 13 patients (43.3%), pregnancy termination occurred after a gestational age of 13 weeks. In 29 of 30 patients, maternal cancer was the reason for termination. In only one patient, the pregnancy was unwanted. In 58 (27.0%) of 215 patients, treatment was delayed until postpartum. Here, the cancer diagnosis was made at a gestational age of 30.6 ± 9.4 weeks. In 122 (56.7%) of 215 patients, a single or a combination of treatment modalities was initiated during pregnancy after a cancer diagnosis at a gestational age of 19.6 ± 8.5 weeks. The distribution of therapies used during pregnancy was as follows: 40.2% surgery (n = 49), 27.0% chemotherapy (n = 33), 20.5% surgery and chemotherapy (n = 25), 2.6% radiotherapy (n = 3), 2.5% surgery and radiotherapy (n = 3), 2.5% surgery, chemotherapy, and radiotherapy (n = 3), 1.6% interferon (n = 2), 0.8% chemotherapy and radiotherapy (n = 1), 0.8% cryotherapy (n = 1), 0.8% hormonal therapy (n = 1), and 0.8% monoclonal antibody

(n = 1). A total of 62 women received chemotherapy and 10 received radiotherapy (Appendix Table A1, online only). The management per gestational trimester is shown in Figure 1A.

Obstetric Outcomes

For the processing of obstetric data, miscarriages (n = 5) and abortions (n = 30) were excluded, leaving 180 pregnancies for further analysis. In 27 (15%) of 180 patients, a gestational complication was registered. The distribution per treatment group is depicted in Table 2. When compared with preterm premature rupture of membranes (PPROM) and preterm labor incidences in the normal population (PPROM, 3%; spontaneous preterm labor, 4%),¹⁴ no increase was seen (PPROM, three [1.7%] of 180; P = not significant, and preterm labor, eight [4.4%] of 180; P = .864 [binomial test]). However, a subanalysis for the patients exposed to chemotherapy and/or radiotherapy revealed a significant increase in preterm labor (eight [11.8%] of 68; P = .012 [binomial test]), but not of PPRM (three [4.4%] of 68; P = .668 [binomial test]). These findings were even more pronounced looking only at chemotherapy-exposed pregnancies (preterm labor, eight [12.9%] of 62; P = .006, and PPRM, three [4.8%] of 62; P = .568 [binomial test]).

Table 3 shows the distribution of the different types of labor and the gestational age at delivery related to the oncologic treatment. Induction of labor or an elective cesarean section was performed in 71.7% (n = 129) of the pregnancies at a mean gestational age of 35.6 ± 2.8 weeks. Maternal cancer was the indication for induction/cesarean section in 76.7% of these pregnancies (oncologic reasons, n = 99; obstetric reasons, n = 21; unknown, n = 9).

Table 2. Obstetric Complications According to Treatment Modality (n = 180)

Treatment Group	No.	%	Complications	Gestational Age at Diagnosis (weeks; +days after treatment)
No treatment (n = 58)	6	10.3	PIH (n = 2)	35.4, NA
			Preeclampsia (n = 1)	NA
			Gestational cholestasis (n = 1)	33.5
			Preterm contractions (n = 1)	36.0
			Antepartum bleeding (n = 1)	23.4
Chemotherapy (n = 33)	13	39.4	Gestational diabetes (n = 1)	29.6
			Preterm contractions* (n = 2)	31.0 (+0), 31.5 (+0)
			PPROM (n = 3)	28.0 (+10), 32.5 (+35), 34.4 (+10)
			Sepsis (n = 1)	26.2 (+0)
			Preterm labor (n = 6)	28.0 (+11), 32.2 (+2), 33.1 (+11), 34.4 (+8), 36.0 (+20), 36.5 (+21)
Chemotherapy + surgery (n = 25)	4	16.0	Preterm contractions* (n = 1)	27.0 (+0 after surgery)
			Sepsis (n = 1)	26.0 (+1 after chemotherapy)
			Preterm labor (n = 2)	34.0, 34.3 (+34 and 59 after chemotherapy)
Surgery (n = 49)	3	6.1	IUGR (n = 1)	NA
			Preterm contractions (n = 1)	30 (NR)
			Sepsis (n = 1)	35.3 (NR)
Radiotherapy (n = 3)	1	33.3	IUGR (n = 1)	28 (+10)
Chemotherapy + radiotherapy (n = 1)	0	0.0		
Radiotherapy + surgery (n = 3)	0	0.0		
Surgery + chemotherapy + radiotherapy (n = 3)	0	0.0		
Others (n = 5)	0	0.0		
Total	27	15.0		

Abbreviations: PIH, pregnancy induced hypertension; NA, not available; PPRM, preterm premature rupture of membranes; IUGR, intrauterine growth restriction; NR, not related.

*Preterm contractions: contractions without cervical changes.

Table 3. Labor Modalities

Labor	All Pregnancies			No Treatment During Pregnancy			Treatment During Pregnancy		
	No. of Pregnancies	%	Gestational Age (mean No. of weeks ± SD)	No. of Pregnancies	%	Gestational Age (mean No. of weeks ± SD)	No. of Pregnancies	%	Gestational Age (mean No. of weeks ± SD)
Spontaneous	41	22.8	38.3 ± 2.4	12	20.7	39.3 ± 1.1	29	23.8	37.8 ± 2.7
Induction	66	36.7	36.5 ± 2.3	18	31.0	37.0 ± 2.8	48	39.3	36.4 ± 2.1
Elective cesarean section	63	35.0	34.7 ± 2.9	25	43.1	35.1 ± 3.1	38	31.1	34.4 ± 2.8
Unknown	10	5.6	—	3	5.2	—	7	5.7	—
Total	180		36.3 ± 2.9	58		36.7 ± 3.1	122		36.1 ± 2.8

Abbreviation: SD, standard deviation.

Neonatal Outcome

Data on the gestational age at delivery were available for 179 of the 185 children—180 pregnancies, with three twins and one triplet. The mean gestational age at delivery was 36.2 ± 2.9 weeks. Delivery occurred for 15 (8.4%) of 179 children before 32 weeks of gestation, for 82 (45.8%) of 179 children between 32 and 37 weeks of gestation, and for 82 (45.8%) of 179 children at term (≥ 37 weeks). For the 97 preterm children, labor started spontaneously in eight pregnancies (8.2%), and induction of labor/cesarean section was performed in 87 (89.7%) with two unknown (2.1%). The indication for induction of labor/cesarean section was maternal cancer for 88%, whereas there were obstetric indications for delivering the baby preterm in 12%.

Data on the birth weight of 175 children were available (166 children from singleton pregnancies, six children from three twin pregnancies, and three children from one triplet pregnancy). In 26 of 175 children, the birth weight was below the 10th percentile for gestational age (14.9%; *P* = .054 [binomial test]). A subanalysis of this group (Table 4) shows a large proportion of small-for-gestational-age children (birth weight below 10th percentile) and children who have hematologic tumors (nine [27.3%] of 33).

Binomial testing revealed a significant increase in small-for-gestational-age children in the group receiving treatment during pregnancy (*n* = 21 [17.9%] of 117; *P* = .012) versus not treated in

pregnancy (*n* = 5 [8.6%] of 58; *P* = not significant). The distribution of the birth weight expressed by percentile for gestational age in the group with and without treatment during pregnancy is presented in Figure 1B. Looking specifically at cytotoxic treatment (chemotherapy and/or radiotherapy), small-for-gestational-age babies were seen in 16 (24.2%) of 66 pregnancies (*P* = .001 [binomial test]) versus 10 (9.2%) of 109 in pregnancies without cytotoxic treatment (*P* = not significant [binomial test]).

The patients in the chemotherapy group who had children with a birth weight below the 10th percentile were treated for acute myelogenous leukemia (*n* = 3), acute lymphatic leukemia (*n* = 1), breast cancer (*n* = 3), Hodgkin’s disease (*n* = 2), and non-Hodgkin’s lymphoma (*n* = 1); the patients receiving chemotherapy and surgery were treated for ovarian cancer (*n* = 2), breast cancer (*n* = 1), and colon carcinoma (*n* = 1). Small-for-gestational-age children of the two patients exposed to radiotherapy were treated for non-Hodgkin’s lymphoma and sarcoma.

Data on the outcome of 175 neonates were available for analysis. A physical abnormality was diagnosed in 13 children at birth (Table 5). Compared with the background risk of major malformations of 4.1% to 6.9% and risk of minor malformations of 6.5% to 35.8%,¹⁵⁻¹⁷ these data do not show an increased incidence of physical malformations at birth. Major and minor malformations were observed in

Table 4. Subanalysis of the Group With Birth Weight Below the 10th Percentile for Gestational Age

Tumor Type	Birth Weight Below 10th Percentile						
	No.	Total No.	%	Treatment During Pregnancy	No.	Total No.	%
Acute lymphatic leukemia	1	3	33.3	Chemotherapy	10	33	30.3
Acute myelogenous leukemia	4	5	80.0	Surgery + chemotherapy	4	25	16.0
Hodgkin’s disease	2	11	18.2	Surgery + radiotherapy	1	2	50
Non-Hodgkin’s disease	2	9	22.2	Surgery	5	46	10.9
Chronic myelogenous leukemia	0	4	0.0	Radiotherapy	1	2	50.0
Hairy cell leukemia	0	1	0.0	No treatment	5	58	8.6
Breast cancer	6	82	7.3	Chemotherapy + radiotherapy	0	1	0
Cervical cancer	2	15	13.3	Chemotherapy + radiotherapy + surgery	0	3	0
GI cancer	2	4	50.0	Other treatments	0	5	0
Brain tumor	2	9	22.2				
Ovarian cancer	2	8	25.0				
Skin tumor	2	16	12.5				
Sarcoma	1	3	33.3				
Other (lung, renal, rhinopharyngeal, thyroid)	0	5	0.0				
Total	26	175	14.9		26	175	14.9

Table 5. Physical Abnormalities Diagnosed at Birth Related to the Treatment Modality (n = 175)

Treatment During Pregnancy	Gestational Age at Treatment (weeks)	Treatment Modality	Malformation	No. of Children With Malformation	Total No. of Children	%
None			Prader-Willi Congenital laryngomalacia Hemangioma	3	58	5.2
Surgery	18 32	Partial nephrectomy + para-aortic lymphadenectomy Mastectomy	Cardiac hematomas in tuberous sclerosis (autosomal dominant genetic disease) Multiple congenital anomalies (hypospadias, agenesis of left little finger, abnormal position of left foot)	3	46	6.5
Chemotherapy	29	Lumpectomy + ALND	Hemangioma	3	33	9.1
	26, 29, 32	AC (3×)	Hip subluxation			
	25, 29, 33	MOPP/ABV (3×)	Pectus excavatum			
Chemotherapy + radiotherapy	24, 28, 32	HOVON70	Hemangioma	1	1	100
	RT: 15-19 CT: 26, 30	Mantle field 40 Gy MOPP/ABV (2×)	Bilateral partial syndactylyl digits II-III			
Surgery + chemotherapy	S: 15	Lumpectomy	Rectal atresia	2	25	8.0
	S: 17	Mastectomy + ALND				
	CT: 20, 23, 26, 29, 32, 35	FEC (6×)				
	S: 17 CT: 23, 26, 29, 32	Lumpectomy + ALND Epirubicin (4×)				
Surgery + chemotherapy + radiotherapy	S: 7	Lumpectomy + SND	Doubled cartilage ring in both ears	1	3	33.3
	S: 9	ALND				
	RT: 11-21	Thorax 50Gy + boost 16Gy				
	CT: 22, 25, 28	FAC (3×)				
Radiotherapy				0	2	0
Surgery + radiotherapy				0	2	0
Other (hormonal, interferon, monoclonal antibody)				0	5	0

NOTE: Bold: major malformations as described by Merks et al.¹⁷
Abbreviations: ALND, axillary lymph node dissection; AC, doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²; MOPP/ABV, mechlorethamine 6 mg/m², vincristine 1.4 mg/m², procarbazine 100 mg/m², prednisone 40 mg/m², doxorubicin 25 mg/m², vinblastine 6 mg/m², bleomycin 10 U/m²; HOVON70, prednisone 60 mg/m² orally (PO; days 1-7), 40 mg/m² PO (days 8-35), 40 mg/m² (days 8-28), methotrexate 15 mg intrathecally (days 1, 8, 15, 29, 43), vincristine 1.5 mg/m² intravenously (IV; days 8, 15, 22, 29, 43); daunomycin 40 mg/m² IV (days 8, 15, 22); cyclophosphamide 1,000 mg/m² IV (day 8), L-asparaginase 6,000 U/m² IV (days 8, 10, 12, 15, 17, 19, 22, 24, 26), mercaptopurine 50 mg/m² (days 29-49), methotrexate 5,000 mg/m² IV (days 29, 43), methotrexate 25 mg/m² PO (day 36), granulocyte colony-stimulating factor (G-CSF) 150 µg/m² (from day absolute neutrophil count [ANC] < 0.5 × 10⁹/L until ANC > 1.0 × 10⁹/L or day 43); RT, radiotherapy; CT, chemotherapy; S, surgery; FEC, fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m²; SND, sentinel node dissection; FAC, fluorouracil 500 mg/m², doxorubicin 60 mg/m², cyclophosphamide 500 mg/m².

five (2.9%) of 175 and eight (4.6%) of 175 neonates, respectively. For the subgroup of patients prenatally exposed to radiotherapy and/or chemotherapy, incidences of malformations were within the normal ranges (major: two [3.0%] of 66 and minor: five [7.5%] of 66).

Two children born 10 days after the administration of chemotherapy for maternal acute lymphatic leukemia (cytarabine + mitoxantrone + intrathecal methotrexate and prednisone + methotrexate + vincristine + daunomycin + cyclophosphamide + L-asparaginase + mercaptopurine), suffered from hematologic toxicity (leukopenia and pancytopenia) and needed hematologic growth factors.

Information on admission to an NICU was available for 172 children. Eighty-eight (51.2%) children were hospitalized in the NICU, and prematurity was the indication for admission in 75 (85.2%) of 88 children. Furthermore, three children (3.4%) were hospitalized because of a congenital anomaly, three (3.4%) because of dysmaturity, one (1.1%) because of respiratory insufficiency, and six (6.8%) for observation.

One instance of intrauterine death was reported in a woman suffering from diabetes whose pregnancy was complicated with gestational hypertension. The patient refused a follow-up at a maternal intensive care unit. At 39 weeks, she consulted a gynecologist with loss of fetal movements and an intrauterine death was diagnosed. During the delivery, a mass was palpated posterior to the vagina which proved to be a newly diagnosed metastasized colon carcinoma. It is unlikely that this fetal loss was directly attributed to the cancer.

DISCUSSION

In this observational study, we report on a large series of patients with cancer diagnosed during pregnancy. The most remarkable finding is the observation that 54.2% of children were born preterm, with a subsequently high rate of admission to the NICU. In the vast majority (89.7%), the delivery was iatrogenically induced. The complications of preterm birth are well studied and include intraventricular hemorrhage, bradycardia/apnea, need for respiratory assistance, necrotizing

enterocolitis, sepsis, seizures, hypoglycemia, and feeding problems. Recently Bastek et al¹⁸ showed that late-preterm neonates (34 to 37 weeks) have significantly more medical complications compared with their full-term counterparts. In addition to these immediate effects, preterm birth is also associated with long-term morbidities and impaired cognitive and behavioral outcomes.¹⁹ In this study, neonatal problems were mainly due to iatrogenic, and therefore preventable, prematurity. Prematurity can be prevented by postponing or continuing treatment until a term delivery can be obtained.

Deliberate delay of therapy to achieve fetal maturity appears to be a safe option for patients with early-stage disease. For early-stage breast cancer, Cold et al²⁰ described the outcomes of a series of 7,501 patients and concluded that there was no evidence for a survival benefit due to early initiation of adjuvant chemotherapy within the first 2 to 3 months after surgery. Nettleton et al²¹ presented a mathematical model to quantify the risk of axillary nodal metastases as a result of delayed treatment of breast cancer during pregnancy. They calculated that the daily increased risk of axillary metastases as a result of treatment delay is 0.028% for tumors with moderate doubling times of 130 days and 0.057% for tumors with rapid doubling times of 65 days. They concluded that this minimal maternal risk may be acceptable to some third-trimester pregnant women with early breast cancer.²¹ Duggan et al²² described planned delay in patients with stage IA and IB cervical cancer with a mean diagnosis-to-treatment interval of 144 days (range, 53 to 212 days). All these patients were free of disease after a median follow-up of 23 months.

Continuation of treatment started during pregnancy is a second way to prevent prematurity. To date, treatment during pregnancy is continued until fetal viability is reached. Instead, fetal maturity should preferably be the criterion to induce delivery. In a multidisciplinary setting, a maximal effort should be made to delay delivery until at least 35 to 37 weeks.

Malformations that were reported in this study are also seen in a normal population. Furthermore, the incidence was not increased. These observations confirm the notion that cytotoxic treatment administered after the first trimester of pregnancy, the period of embryogenesis, does not result in a higher incidence of congenital malformations.^{4,6-9,23}

Two children born 10 days after high-dose chemotherapy for acute lymphatic leukemia developed a neutro/pancytopenia. Neonatal bone marrow insufficiency after prenatal chemotherapy exposure was described previously.^{4,24} The hematologic toxicity in the two children suggests that a considerable fraction of these drugs passes through the placenta. In literature on cancer treatment during pregnancy, growth restriction is a permanent concern^{4,24,25} which is confirmed by the findings in this study. The largest proportion of small-for-gestational-age children was seen in patients with hematologic tumors.

Ring et al⁶ described a series of pregnant women with breast cancer treated with chemotherapy during pregnancy. Data on birth weight were available in 17 children, and they were all above the 10th percentile for gestational age. Also in this study, the birth weight in breast cancer patients receiving chemotherapy in pregnancy was within normal ranges (4 of 34 children had a birth weight below 10th percentile of gestational age). Since small-for-gestational-age children were observed only in mothers with certain tumor types such as hematologic tumors but not in mothers with breast cancer, the data suggest that an impact on fetal growth might be related to specific

cancer types and treatments. Whether the effect is determined by the maternal illness that is associated with malnutrition and a catabolic status,²⁶ or by direct or indirect effects of the treatment remains an unanswered question.

Patients receiving chemotherapy had an increased risk of preterm labor. However, the time interval between the administration of chemotherapy and the onset of contractions varied substantially. The underlying mechanism is unclear. Physical or psychological stress can induce preterm labor through activation of the maternal hypothalamic-pituitary-adrenal axis;²⁷⁻²⁹ thus, the stress associated with cancer diagnosis and treatment may contribute. Alternatively, fetal stress or uteroplacental vasculopathy may activate the fetal hypothalamic-pituitary-adrenal axis and induce labor.³⁰ The potential role of chemotherapy in preterm labor needs additional investigation. Apoptosis in amnion epithelial and chorion trophoblast layers of fetal membranes is known as an important factor in the pathogenesis of membrane rupturing.^{31,32} This process theoretically might be facilitated by exposure to chemotherapy.

It is accepted that interruption of pregnancy is indicated in instances of a poor maternal prognosis or when there is an urgent need for cytotoxic treatment in the first trimester.^{4,13,25} In this study, the main indication (in 29 of 30 patients) for pregnancy termination was a maternal malignancy. Seventeen of these pregnancies were diagnosed in the first trimester. Of the 13 pregnancies that were ended thereafter, eight had a poor maternal prognosis at diagnosis. One patient had a stage IB1 cervical cancer diagnosed at 15 weeks for which therapy during pregnancy is still considered experimental. In four patients, the pregnancy was terminated because of the need for oncologic treatment while, according to current knowledge, this was medically not strictly indicated. Surgical and medical treatment for breast cancer (n = 3; T1-2 at 19, 20, and 22 weeks) and Hodgkin's disease (n = 1; 20 weeks) is possible during pregnancy. The fact that three of these four instances of pregnancy termination were treated in the same city emphasizes the need for sufficient information and education on this topic.

The most frequently encountered tumor types were breast cancer, hematologic malignancies, skin cancer, and cervical cancer. The frequencies follow the distribution of cancer in the general population in this age group (20 to 40 years) in this area.³³ Other studies on cancer during pregnancy described proportionally more cervical cancers (maximum of 15%), malignant melanomas (maximum of 31%), or thyroid cancer.^{11,13,34} Differences in inclusion criteria and regional differences in incidence, sensitization campaigns, and screening programs might explain the difference between our study and others. Because tumor distribution is comparable to that in the nonpregnant population of that age group, we can conclude that the concurrence of cancer and pregnancy most likely reflects the patients's age (mean age of 33 years).

An important strength of this study is that a large series of only invasive cancers diagnosed during pregnancy was included (excluding preinvasive and postpartum diagnoses). Furthermore, the interpretation of the birth weight was adjusted for gestational age and sex. Limitations to our study include the absence of centralized national registries for the entity "cancer and pregnancy." Second, there is no separate registration for termination of pregnancy in most hospitals. Therefore, we can assume an under-registration of the early pregnancies that miscarried or were interrupted.

The findings of this study show an overall good outcome of pregnancies complicated with cancer. However, a high rate of preterm labor induction with a subsequent high rate of admission of infants to the NICU was observed. Interdisciplinary decision making on the timing of delivery by obstetricians and neonatologists is necessary. Preferably, delivery should not be induced before 35 to 37 weeks. Current data confirm that cytotoxic treatment administered during the second and third trimesters of pregnancy does not increase the rate of congenital malformations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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