Cancer in pregnancy: maternal and fetal implications on decision-making

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Summary

Background: Cancer complicates one out of 1,000 pregnancies. No standardized therapeutic interventions have been reported for these patients. *Methods*: Fifteen patients with cancer during pregnancy were diagnosed between 6.5 and 36 weeks of gestational age between January 1991 and December 2007. *Results*: Among the 15 cases one patient with early diagnosis (11 weeks) asked for interruption of pregnancy, two patients rejected chemotherapy in order to avoid fetal effects, seven patients underwent surgery during the first or second trimester, and two patients agreed to start the treatment only after delivery. Standard platinum-based chemotherapy (cisDDP) was postponed in six patients to the second trimester (administered after surgery in 2 cases). Chemotherapy was started between 18.3 and 29.6 weeks (median 22.3 weeks). One patient had pPROM (22.3 weeks) after chemotherapy with cisDDP. Ten patients were delivered by elective cesarean section and three by vaginal delivery. Mean gestational age at delivery was 33.5 weeks (range 32.1-40.0); mean weight at birth was 2,550 g (range 1,250-3,450). None of the newborns showed congenital malformations, and all had normal Apgar scores. Anemia occurred in two newborns. At a median follow-up of 56 months (range 2-198 months) all children were well and healthy. Eleven out of 15 mothers are alive and well, and one is alive with disease. An advanced neoplasm was diagnosed in three patients who died. *Conclusion*: When platinum-based chemotherapy is administered during the 2nd-3rd trimester, adverse effects in newborns are comparable to those in the general population. Deliberate treatment delay to achieve fetal viability or to improve fetal outcome may be reasonable for patients with early-stage cancer.

Key words: Cancer; Pregnancy; Fetal outcome; Chemotherapy; Surgery; Radiotherapy.

Introduction

Cancer complicates between 0.1 and 0.7% [1-3] of all pregnancies: the incidence is expected to rise with the concomitant increasing age of childbearing [4]. The most common malignancies observed include breast cancer (37/1,000), thyroid (33/1,000), cervix (16/1,000), ovary (15/1,000), and colon, malignant melanoma, malignant lymphomas and leukemia which have an ascending incidence curve in the reproductive years [5]. No standard therapy has been proposed to date. Similar cases are reported as occasional, or form limited studies. Among potential interventions, none have been prospectively evaluated for treatment efficacy in the mother or safety for the fetus.

The limited information available concerning the best management of a pregnant woman with cancer poses a difficult dilemma to the woman, her family and to the medical staff, it also raises many psychological and ethical issues: how the pregnancy influences the behavior of the disease and how the latter, and the associated treatment, affect the pregnancy. Management decision-making depends on the mother's attitude toward pregnancy, gestational age at diagnosis, stage of the disease, and desire to preserve fertility. During pregnancy, the use of chemotherapy, radiotherapy or surgery are controversial due to the potential adverse effects on fetal growth and health. Most patients experiencing cancer during pregnancy are potentially candidates for chemotherapy or multimodality treatment.

Case Reports

Clinical findings

In this retrospective analysis, 13 patients with a diagnosis of cancer during pregnancy were selected between January 1991 and December 2007 regardless of whether or not they received specific medication.

All cases were managed and treated at the Gynecologic Oncology Unit and the Obstetrics Department, University of Brescia.

All patients were followed throughout their pregnancies by obstetricians and gynecologic oncologists experienced in high-risk pregnancies and neoplastic diseases. Patients were kept fully informed and treatment strategies were planned and carried out taking into consideration each patient's decisions. All patients were carefully counselled about treatment options.

Treatment decision-making was based on several items: gestational age, fetal risks concerned with treatment, stage and prognosis of the disease, the patient's medical condition, and the patient's desire for pregnancy.

All patient information connected with this study was collected from the medical records. We selected data regarding the disease, such as histopathologic diagnosis, stage, timing and kind of treatment, and data regarding the pregnancy, with particular care about complications.

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Table 1. — *Clinical features of pregnant patients*.

Case No.	Age yrs	Gestational age at diagnosis (weeks)	Cancer	Stage	Gestational age at treatment (weeks)	Treatment	CT	Maternal outcome
1	41	6.5	ovary	IIB	8.3	Surg		AWD
2	36	11.0	cervix	IB2				NED
3	35	14.0	ovary	IC	14.0	Surg		NED
4	33	16.0	brain		16.0	Surg		NED
5	21	13.3	ovary	IIIA	18.3	Surg/CT	cisDDP	NED
6	28	20.2	cervix	IB2	21.2	CT	cisDDP	NED
7	39	18.4	colon	IV	22.5	Surg		DOD
8	34	20.5	cervix	IIA	23.5	CT	cisDDP/ VCR	NED
9	36	7.0	ovary	IC	18.6	Surg/CT	cisDDP	NED
10	38	26.1	liver	IV		Postponed		DOD
11	42	24.5	cervix	IB2	27.5	CT	cisDDP	NED
12	41	26.3	urethral	T2N0M0	29.6	CT	cisDDP	NED
13	37	36.0	cervix	IB2		Postponed		NED
14	38	30.0	cervix	IIB		Postponed		DOD
15	37	22.0	ovary	IA	24	Surg		NED

cisDDP: cis-diamminedichloroplatinum - VCR: vincristine - Surg.: surgery - CT: chemotherapy - AWD: alive with disease - DOD: died of disease - NED: no evidence of disease.

Diagnosis of cancer was made during physical and ultrasonographic examination planned for pregnancy or, in four cases, in relation with symptoms. Biopsies confirmed the neoplastic lesions in all cases.

Four patients were diagnosed in the first trimester, six in the second, and three in the third trimester of pregnancy.

The mean maternal age at diagnosis was 36 years (range: 22 to 42). Gestational age at diagnosis ranged from 8.3 to 37 weeks (mean 19 weeks) (Table 1).

Fetal outcome was assessed with birth weight, Apgar score (a 5-min Apgar score of 7-10 was considered normal) [6] and neonatal complications and pediatrician assessment of possible congenital malformations from hospital records. Prematurity was defined as delivery occurring at a gestational age of less than 37 weeks [7, 8] (Table 2).

Children were extensively followed-up. Physical and neurological development and clinical history were investigated. School performance and secondary sexual development were documented for the older children.

Clinical features of pregnant patients are listed in Table 1.

Cervical carcinoma

Six cases of cervical cancer were observed:

Patient 2: presented a diagnosis of squamous cervical carcinoma, Stage IB2 at 11 gestational weeks (GW). The woman's preference was to terminate the pregnancy although an alternative option was offered and discussed. Afterward she underwent neoadjuvant chemotherapy (paclitaxel and cisplatinum) followed by radical surgery.

Patient 6: presented a diagnosis of squamous cervical carcinoma, Stage IB2 at 20.2 GW. Eight days after the administration of the first course of chemotherapy, 90 mg of cisDDP (50 mg/m^2), she was admitted to the hospital with extremely preterm premature rupture of the membranes (pPROM), which led to miscarriage within a few hours. Microbiological vaginal culture was negative. Chemotherapy was restarted seven days later, with the addition of paclitaxel (175 mg/m^2). Chemotherapy was followed by radical surgery and adjuvant pelvic radiation for positive pelvic nodes. The patient was alive without evidence of disease two years after diagnosis.

Patient 8: at 20.5 GW was diagnosed with squamous cervical carcinoma Stage IIA. She received neoadjuvant chemotherapy with cisDDP 200 mg/m^2, VCR 4 mg, in four courses starting at 23.5 GW. Cesarean section was performed at 32 GW, 22 days after the last chemotherapy cycle. Concomitant with the cesarean section radical hysterectomy with pelvic lymphadenectomy was performed. The patient was alive without evidence of disease 13 years after diagnosis.

Patient 11: presented a diagnosis of squamous cervical carcinoma Stage IB2 at 24.5 GW. She underwent neoadjuvant chemotherapy with cisDDP 180 mg/m^2, in three courses, starting at 27 GW. Cesarean section was performed at 36 GW, 14 days after the last chemotherapy cycle. In the same surgical session radical hysterectomy with pelvic lymphadenectomy was performed. The patient is alive without evidence of disease three years after diagnosis.

Patient 13: presented a diagnosis of cervical cancer at 36 GW. Histological examination revealed an endocervical mucinous adenocarcinoma, Stage IB2. Cesarean section was performed at 40 GW; 14 days later she underwent neoadjuvant chemotherapy followed by radical surgery. After one year she was alive and well.

Patient 14: presented a Stage IIB cervical cancer at 30 GW. After a cycle of corticosteroid for fetal lung maturity induction, a cesarean section was performed. As a consequence of pelvic lymph nodal spread chemoradiation treatment was planned after surgery. The patient died of diesease 32 months after treatment.

Ovarian cancer

Five cases of ovarian cancer occurred during pregnancy:

Patient 1: underwent right salpingo-oophorectomy by laparotomy at 6.5 GW for an adnexal mass which was later diagnosed as granulosa cell tumor Stage IIB. The patient decided to continue the pregnancy and to delay any chemotherapeutical treatment after delivery. After a cesarean section the patient received five courses of cisDDP, vinblastin and bleomycin. Fifteen years later the patient developed abdominal recurrence and, after surgical debulking, she is still in treatment with chemotherapy.

Patient 3: a persistent right ovarian mass was detected at 14 GW and subsequently removed by laparoscopic salpingo-oophorectomy. Stage IC mixed epithelial ovarian tumor of mucinous and endometrioid origin was detected. Adjuvant chemotherapy was considered postponable. The patient had a late preterm labor and delivered vaginally at 34.4 GW. After five months she was alive without evidence of disease.

Table 2. — *Fetal outcome*.

Case No.	Gestational age at delivery (weeks)	Type of delivery	Neonatal weight	AS	Toxicity	Fetal outcome	Age at follow-up	Abnormal development
1	35.6	CS	3550	9/10	no	Well	07/1991	no
2	11.0					Interruption		
3	34.4	VD	2960	9/9	no	Well	05/2008	no
4	37.5	CS	3030	9/9	no	Well	01/2007	no
5	35.6	CS	2690	9/10	anemia	Well	02/1995	no
6	22.3					Misc.		
7	33.2	VD	1840	8/9	no	Well	09/2002	no
8	32.1	CS	1690	5/8	anemia	Well	06/1995	no
9	34.0	CS	1970	7/10	no	Well	12/2007	no
10	34.0	CS	2490	9/9	no	Well	12/2005	no
11	36.0	CS	2590	7/9	no	Well	01/2006	no
12	33.2	CS	2370	8/8	no	Well	01/2007	no
13	40.0	CS	3270	9/9	no	Well	08/1999	no
14	30.0	CS	1250	7/9		Well	03/2007	no
15	40.0	CS	3270	9/9		Well	05/1999	no

AS: Apgar Score - VD: Vaginal delivery - CS: Cesarean section

Patient 5: a Stage IIIA papillary-serous ovarian borderline tumor, with omental invasive implants, was diagnosed at 13 GW by laparoscopic right salpingo-oophorectomy and surgical staging. Chemotherapy with cisDDP 450 mg/m^2 in six courses was started at 18.3 GW. Cesarean section was performed at 35.6 GW. Two years later the patient underwent laparoscopic left salpingo-oophorectomy for a 4 cm ovarian mass. Histopathological analysis revealed a papillary-serous ovarian borderline tumor. The patient, to date, is alive after 12 years with no evidence of disease.

Patient 9: an ovarian mass was detected by routine pelvic ultrasound examination and the patient underwent laparoscopic left-oophorectomy at 7 GW. A Stage IC endometrioid adenocarcinoma was diagnosed. Adjuvant chemotherapy started at 19 GW with cisDDP 175mg/m^2 in five courses. Delivery was performed at 34.3 GW by cesarean section concurrently with hysterectomy, residual oophorectomy, omentectomy, lymphadenectomy, multiple biopsies and peritoneal washings. The patient is in complete remission at 18 months.

Patient 15: the patient presented a 8 cm vascularized atypical adnexal mass at 22 GW. Laparotomic unilateral salpingo-oophorectomy with frozen section was performed. Following the intraoperative diagnosis of malignant intracystic mucinous carcinoma of the ovary, surgical staging was performed. The definitive diagnosis was: Stage IA well differentiated mucinous carcinoma of the ovary. The patient delivered at term a healthy baby. CT scan was negative a month after delivery. The patient is in follow-up with no evidence of disease.

Colorectal carcinoma

Patient 7: presented at diagnosis a Stage IV colorectal carcinoma with multiple peritoneal metastases at 18.4 GW. For the advanced disease, with an expected low survival rate, no chemotherapy was administered. The patient underwent palliative surgery at 22.5 GW to avoid intestinal obstruction. She had a preterm labor and delivered vaginally at 33.2 weeks of gestation. She died a few months afterward.

Brain tumor

Patient 4: presented with a persistent headache in early pregnancy with no other apparent symptoms. After a few weeks MRI revealed a cerebral mass. She underwent neurosurgical resection at 16 GW. Histological analysis diagnosed a focal astrocytoma. The patient delivered at 37.5 weeks by cesarean section. After one year she was alive and well without disease.

Liver carcinoma

Patient 10: was diagnosed with a primary neoplasia of the liver at 26.1 GW during diagnostic procedures for liver dysfunction. MRI showed advanced disease, bioptically confirmed as Stage IV liver cancer. Considering the high mortality rate due to the extent of hepatic resection required, surgery was not recommended. Cesarean section was performed at 34 GW. She died four months after delivery.

Urethral carcinoma

Patient 12: presented with persistent hematuria, dysuria and recurrent urinary tract infections. Physical examination revealed an urethral neoplasia. Biopsies revealed clear cell adenocarcinoma. Neoadjuvant chemotherapy with cisDDP started at 30 GW, and 135 mg/m^2 total were administered throughout three courses. Cesarean section was performed at 33.2 GW. Subsequent surgery was performed, including an *en bloc* total cystectomy, removal of the anterior wall of vagina and of the distal and proximal urethra, pelvic lymphadenectomy and bladder reconstruction. After one year she was alive without disease.

Fetal outcome

Among the seven cases in which surgery was performed during pregnancy (patients 1, 3, 4, 5, 9 and 15), six underwent abdominal surgery, three of which were within the 14 GW. The aim of intervention was fulfilled in all seven cases, and no obstetrical complications arose.

In six cases (patients 5, 6, 8, 9, 11, 12) the fetus was exposed to chemotherapeutic agents.

No obstetrical complication was observed except a spontaneous abortion (pPROM).

In patients treated with chemotherapy, delivery was planned after a mean of 19 days after the last cycle.

Apgar scores at one min ranged from 5-9 and at 5 min from 8-10.

Newborn weight ranged from 1,250 to 3,450 g, all of which were within normal range for gestational age. No congenital malformation in any newborn was diagnosed. Hearing-evoked potentials and neurologic follow-up were normal. Anemia occurred in two newborns which was successfully treated with blood transfusion. No other effects have been observed in the infants.

The mental health of children exposed to chemotherapeutic agents in utero were investigated and none presented any behavioral or cognitive disorder.

At a median follow-up of 56 months (range 2-198 months) all children were well and healthy. In five children the neurological development at an older age (6-7 years old) was normal, with a normal scholar performance.

No case of placental or fetal metastatic involvement originating from maternal cancer was observed.

Discussion

The management of cancer in pregnancy implies many clinical and ethical issues. First of all, the typical standard management for any specific malignancy is often not applicable since it would directly affect the pregnancy. For abdominal tumors, the presence of a pregnant uterus constitutes a technical problem both for an adequate surgery and radiation therapy. However, even if chemotherapy is technically feasible at any gestational age, concerns often arise regarding possible adverse effects on the fetus. Therefore, clinicians should carefully consider several aspects such as stage, site of tumoral spread, maternal and fetal prognosis and, obviously, gestational age. The decision should consider the patient's condition and treatment options. Therapeutic indications should refer primarily to the necessity for treatment, which is mainly related to prognosis, with careful evaluation of the options, which depend mostly on the gestational age [9]. The clinical management is to be evaluated case by case trying to balance the risks and severity of fetal adverse effects with the benefits linked to an adequate treatment. The timing of delivery should be carefully planned, evaluating which treatments can be performed during pregnancy and which are not feasible and therefore postponed.

As far as surgery is concerned, two different aspects should be taken into consideration: surgery itself and anesthesia. While the latter is a general issue, regardless of the kind of intervention, the former brings a number of problems related to the type and extent the treatment requires and may differ from case to case.

Surgical interventions may present some risk to the fetus, especially laparotomic surgery for abdominal disease. During the first trimester abdominal surgery appears to be somewhat more hazardous [10]. However, the bigger volume of the uterus in second and third trimesters may constitute a technical problem for surgical procedures. Complications in surgery during pregnancy are usually related to maternal anemia, lower tolerance to hypoxyemia and reduction in functional residual capacity. During surgery the fetus is exposed to the transplacental effects of anesthetic agents [11]: however, with the modern anesthetic techniques many problems can be very well handled with minimal risk to the fetus. Surgery may create a stress event directly on the mother and the fetus and it can trigger preterm labor, so it is preferable, whenever possible, to wait until the third trimester. Extra-abdominal surgery seems to interfere minimally with pregnancy [10]. For women affected by breast cancer during the first and second trimesters, radical mastectomy and axillary dissection may avoid the need for radiation; during the third trimester treatment options can be based on conservative breast surgery followed by radiation after delivery. Surgical treatment can be performed on pregnant women affected by more rare tumors of the brain, thyroid, bladder or kidney and colorectal cancers [12]. Surgical treatment for ovarian cancer can be performed by open surgery or the laparoscopic technique [13, 14]; tumor mass excision, unilateral or bilateral salpingo-oophorectomy are usually feasible.

We have reported seven cases of surgery during pregnancy. In one case (brain tumor, patient 4), pregnancy did not alter the surgical procedure in any way. In another case (colon cancer, patient 7), the management was not affected by pregnancy since a palliative intervention was required. In the five cases of ovarian disease (patients 1, 3, 5, 9 and 15), surgery was modulated by balancing the need for an adequate staging and the desire to continue the pregnancy. Therefore laparoscopic or laparotomic removal of the affected ovary with accurate exploration of abdominal organs, multiple random peritoneal biopsies and cytological analysis of peritoneal washings was performed, postponing any other procedure such as hysterectomy or lymphadenectomy after delivery. No surgery-related complications were reported in our cases.

During pregnancy several changes occur in the physiology of several organs, which in turn lead to modifications in pharmacodynamics of many drugs. The increased blood volume and increased renal clearance might decrease active drug concentrations; while the faster hepatic function and changes in the gastrointestinal system may also affect drug absorption and peak concentrations [15].

Many chemotherapeutic agents are listed in the Food and Drug Administration pregnancy category D, because there are data on pregnant women indicating potential risk to the fetus [16]. The teratogenic properties of many drugs depend on the timing of exposure, the dose and the characteristics of placental transfer. Placental pharmacokinetics leads to potential toxicity to the fetus. Recent pharmacogenomic studies confirm that the presence of MRP-related proteins in the syncytiotrophoblast play an important role in fetal "chemoprotection" from antiblastic drugs, like cisplatin and vincristine [15-17]. The placenta, in fact, retains the capacity to bioinactivate pharmacologically active molecules and secrete them in the maternal circulation. The placenta presents a crucial role as a barrier to cytotoxic agents and an active filter for the fetal blood, thus the time of delivery must be chosen carefully, allowing some time to pass before proceeding to the cesarean section [17, 18].

Malformations are related to the gestational age at exposure. The incidence of fetal malformations for first-trimester chemotherapy exposure with a variety of agents ranges from 14% to 19%. Organogenesis is complete after 12 weeks with the exception of the brain and gonads. When exposure occurs in the second or third trimester the incidence of fetal malformations drops to 1.3%. Cytotoxic drugs administered in the second and

third trimesters are not teratogenic [19, 20], but may lead to intrauterine growth restriction (IUGR), prematurity and stillbirth [21]. Cisplatin is the most important agent for many gynaecologic cancers. Sensorineural hearing loss was reported by Raffles in a child born at 26 weeks, after exposure to this drug six days before delivery [22] but many reports suggest that most of children exposed in utero to cisplatin during the second or the third trimester did not present any malformation [23-26].

We have reported six cases of chemotherapy administered during pregnancy. We considered it safe to postpone the first administration of chemotherapy from 18 GW and on. In two cases (cases 5 and 9) when cancer was diagnosed during the first trimester, we postponed the treatment, respectively, for five and 12 weeks in order to reach 18 GW. In the other four cases (cases 6, 8, 11 and 12) cancer was diagnosed in the second and third trimesters, therefore the treatment was started immediately. Drugs, doses and schedules employed were adequate, according to type and stage of the disease.

Another patient (case 1) agreed to receive chemotherapy only after delivery, postponing the treatment at 26 weeks, even though we suggest starting as soon as 18 GW.

The effects of radiation exposure, including radiation therapy, are principally related to the dose received, the field of irradiation and the week at the time of exposure [27]. Exposure during the preimplantation phase from day 0 to day 14 is likely to cause miscarriage during organogenesis from weeks three to eight results in a wide range of congenital malformations and the greatest growth restriction. Exposure during the fetal stage from weeks eight or nine to 40 leads to growth restriction [28]. Daly's review of medical exposure suggests that radiation exposure during organogenesis is predominantly associated with mental retardation [29]. Risk as a function of dose is quantified in the American Association of Physicists in Medicine report on fetal dose from radiotherapy: ideal dose to the fetus should be kept below 0.05 Gy [30]. The site of the tumor is obviously one of the most important factors in pregnancy. The greatest determinant of dose is the distance from the field edge, with dose falling roughly exponentially with distance: pelvic fields would result in abortion. It is possible, however, to treat non-pelvic fields and allow the pregnancy to continue without increased risk of deterministic effects by ensuring that the dose to the fetus is below 0.1 Gy [31]. Although the risk of carcinogenesis cannot be excluded, the risk below this dose is extremely low.

In our series no patient had indications for radiation therapy during pregnancy.

Conclusion

Malignant disease during pregnancy raises a conflict between optimal maternal therapy and fetal well-being. Each patient should be evaluated individually, considering both the aggressiveness of the cancer and the gestational age when the therapy is applied. Many authors today suggest that treatment of cancer in pregnant women should adhere to the same criteria as in non-pregnant patients with the required modifications due to the pregnancy. However it has been suggested that therapeutic abortion should be offered to all patients who develop cancer during the first trimester.

Our data suggest that pregnancy is not adversely affected by treatment. Modern techniques in surgery and anesthesiology allow a safe and generally adequate surgical approach, when it is required. Surgery, even in the first trimester, can be safe and should be considered as diagnostic time or, if necessary, primary treatment.

Chemotherapy should be performed with fetal surveillance and monitoring. Exposure to antiblastic drugs during the first trimester increases the risk of spontaneous abortion, fetal death, and major malformation [15] while during the second and third trimester, increases the risk of IUGR and low birth weight. Exposure to antiblastic drugs *in utero* does not affect neonatal morbidity or mortality even if further follow-up is required to determine any potential long-term effects.

There is little doubt that gestational age exerts an influence on outcome of prenatal births and infants, when compared with those born at term, having higher rates of mortality and neonatal morbidity. In our series the delivery timing was planned in relation to gestational age, stage of the disease and its curability. The time of delivery, planned after 32 GW, took place in a perinatal center experienced in high-risk pregnancies. Delivery was delayed by two to three weeks after chemotherapy to allow the bone marrow to recover. No cases of malformation or small for gestional age at the delivery were reported.

Deliberate delay of treatment to achieve fetal viability or to improve fetal outcome would be reasonable for patients with early-stage cancer with a good prognosis, whereas treatment delay in advanced cancer raises concerns about maternal morbidity [9].

Pregnant woman with cancer must be informed about the lack of evidence regarding long-term consequences of *in utero* chemotherapy exposure.

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