Cancer in Pregnancy: Results of a Series of 32 Patients

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Abstract. *Background: Cancer complicates approximately 1 in 1000 pregnancies. In pregnancy management, whether the benefits outweigh the risks derived from therapy must be carefully considered. Materials and Methods: Thirty-two pregnant patients with the diagnosis of malignancy were followed. The indications and timing for surgery, chemotherapy, radiotherapy or delayed treatment were decided according to the malignancy characteristics and gestational age. The patient's consent was obtained before every decision. Results: The rate of live births, premature deliveries, foetal abnormalities and neonatal deaths was 97%, 82%, 9% and 3%, respectively. Three women (9%) died during puerperium because of disease progression. Conclusion: The cancer treatment took into full consideration the specific condition of each pregnant patient. A good rate of live births was observed, even if a high rate of preterm delivery occurred. The management of malignancy required a team of experts in order to optimise every available choice for maternal health and neonatal well-being.*

Cancer is the leading cause of death in women of reproductive age (1). It is estimated that 1 per 1000 women will be affected by cancer while pregnant (2). The most common malignancies associated with pregnancy are cervical, breast, melanoma, ovarian and haematological cancers, as well as leukaemia and lymphoma (3).

There are no convincing data that pregnancy adversely influences the biology, natural history, prognosis or treatment of maternal cancer (4). The evaluation and treatment of pregnant women with cancer is generally similar to that of non-pregnant women with a few exceptions. The risks associated with chemotherapy or radiotherapy depend on the gestational age and the dose of antineoplastic agents and X-rays (5). The therapeutic challenge becomes critical when the immediate intervention for maternal indication *versus* delayed therapy for foetal indication must be evaluated (6).

Radiation therapy is an effective treatment modality for a variety of cancer encountered during pregnancy. The developing embryo and foetus are extremely sensitive to ionising radiation, with the human brain apparently the most sensitive organ. However, the effects of exposure are dose- and time-dependent. The risks of foetal exposure to X-rays have been the subject of numerous studies over the last 50 years. The lack of clear information has given rise to unjustified panic among the public (7). The possible embryonic or foetal damage from radiation may be classified into three principal types. The first type is lethal. In fact, exposure to high-energy radiation may induce cytogenetic abnormalities that will result in a spontaneous abortion (4). The second type is teratogenic, or abnormal foetal development, which may occur on exposure to radiation in the first 12 weeks of pregnancy during organogenesis. The congenital malformations, most frequently described with exposure to high doses of radiation, involve the central nervous system (CNS), skeletal and genital systems. Other malformations include eye abnormalities, such as microphthalmia, retinal changes and cataracts. Furthermore, later in gestation exposure to high-dose radiation will result in foetal growth retardation and neurophysiological and behavioural changes that may become obvious in infancy or childhood. The third and last type of damage is carcinogenic: malignancy may be induced due to radiation exposure in the second and third trimesters of pregnancy, these effects becoming evident in the first decade of life (4). The available data reveal that CNS malformations and foetal growth retardation occurred following acute exposure to >50 rad. Foetal exposure to <5 rad (maximum dose for diagnostic examination is 3) has not been associated with such effects. Many radio-diagnostic procedures, such as regular radiographs, radioisotopes scan and computed tomograms used in the pre-treatment evaluation of different malignancies, are associated with radiation exposure to the mother and, potentially, the

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Key Words: Pregnancy, radiotherapy.

foetus. If malignancy is suspected, it is fully justified to perform diagnostic examinations (8). Radioactive iodine should not be used for therapy in pregnancy because iodine can cross the placenta and cause foetal hypothyroidism and cretinism (4).

Chemotherapy is an essential part of the treatment for many malignancies that can occur during pregnancy. Before initiating treatment with antineoplastic agents in a pregnant woman, the potential benefits to the mother should be weighed against the potential risks both to the foetus and to the mother. The time of foetal exposure to the chemotherapeutic agent (s) is a very important determinant of foetal outcome (9). In the first trimester, exposure to chemotherapy drugs can result in congenital malformations and/or spontaneous abortions. The risk of congenital malformations has been reported to be as high as 17% (10), but this rate can vary from agent to agent. The folic acid antagonists, aminopterin and methotrexate, seem to be more teratogenic than other antineoplastic agents (11). A syndrome of congenital anomalies that includes cranial anomalies, cleft palate, anencephaly and micrognathia has been associated with the use of aminopterin (12). The use of alkylating agents and procarbazine has also been associated with the teratogenic effect (13). With regard to the use of anthracyclines in pregnancy, a recent paper (14) showed a rate of 11% of foetal malformation if used in the first trimester. Their foetal toxicity during the second and third trimesters was documented with a rate of 2% for cardiac toxicity and 4% for bone marrow depletion. Furthermore, second and third trimester exposure to chemotherapy has been associated with low birth weight, foetal growth retardation, intrauterine death, premature births, microcephaly, mental retardation and impaired learning behaviour. Total parenteral nutrition could be helpful in the presence of severe maternal malnutrition and could also improve and sustain foetal growth (15). In some cases, chemotherapy medication could be indicated, without any previous testing on pregnant patients (16).

Maternal complications such as thrombocytopenia and/or leucopenia at the time of the delivery can determine the possibility of massive haemorrhage and serious infections. Therefore, the timing of delivery should be well planned out in a patient treated by chemotherapy (4). The aim of this study was to retrospectively review our experience in the treatment of cancer in pregnant women. The outcome of pregnancy and neonatal well-being were also investigated.

Materials and Methods

In the last 12 years, 32 cases of pregnant women with cancer were followed in our centre. The malignancies differed in histological type, grade, size and stage (Table I). Haematological malignancies were the most frequent (n=11), followed by breast cancer (n=7), ovarian cancer (n=3), cervical cancer (n=3), astrocytoma (n=2), and colon cancer (n=2). Furthermore, single cases of tongue cancer, jaw cancer, melanoma and gastric cancer were encountered. Surgery, chemotherapy and radiotherapy or delayed treatment were employed according to each case. Accurate counselling was given to the couple and the patient's consent was obtained before every decision. Maternal treatment was decided on by a team of experts (obstetricians, oncologists, radiotherapists, haematologists, surgeons and neonatologists).

Total parenteral nutrition was used in five cases, when the maternal nutritional requirements could not be met by the oral diet.

Maternal and infant follow-ups were carried out between 4 months to 1 year after delivery.

Results

The treatment of cancer in pregnant women according to the gestational age at the time of diagnosis is shown in Table I. The mean gestational age at diagnosis was 20 weeks ±9. One woman had a twin pregnancy. In two-thirds of the cases, the diagnosis of malignancy was made in our centre. In one-third of the cases, the diagnosis was made elsewhere, but the patients decided to be followed in our ward for personal reasons.

When the diagnosis of malignancy was made in the first trimester (nine cases), surgery was performed in three cases (astrocytoma and two cases of breast cancer) and radiotherapy was performed in one of them (astrocytoma). In six cases, treatment was delayed until the second or to the third trimester.

In cases occurring in the second trimester (15 cases), surgery was performed in five cases, radiotherapy in one and chemotherapy in eight. In three cases, treatment was completed in puerperium by chemotherapy or radiotherapy. In another two cases (13%), treatment was delayed until after delivery.

When the diagnosis of malignancy was made in the third trimester (eight cases), surgery was performed in one case and chemotherapy in two. The decision to delay treatment was taken in five cases (63%).

The employment of total parenteral nutrition in pregnant patients allowed delivery to be postponed to a period compatible with foetal viability.

Three maternal deaths (9%) were observed during puerperium because of progressive disease. In these cases, the tumour had been very advanced at the time of diagnosis and it had been necessary to plan a preterm delivery.

The pregnancy outcomes are shown in Table II. A vaginal delivery was performed in 8/32 patients (25%), while 24 patients underwent a caesarean section (75%). There were 32/33 live births (97%). There was also one set of twins who were born normal and healthy. Preterm infants (≤36 weeks of gestation) included 27/33 cases (82%); the rate of low-birth-weight infants (<2500 g) was 22/33 (67%). The gestational age at delivery was equal to 33±4 weeks; the

Table I. *Cancer in pregnancy: our series of patients.*

Patient	malignancy	Gestational age at diagnosis (wks)	Treatment
1	CML	4	αINF (20-27 weeks), Hydroxyurea (27 weeks)
2	Astrocytoma	5	Surgery (5 weeks) + Rt (10-17 weeks)
3	Breast cancer	6	Surgery (10 weeks) + Adriblastine (20-23 weeks)
4	Breast cancer	8	Surgery (8 weeks) + AC (14-22 weeks and in puerperium)
5	Cervical cancer	8	Surgery (28 weeks)
6	Cervical cancer	12	L--EEP (29 weeks)
7	Tongue cancer	13	TPN, Rt (24-33 weeks)
8	HL	13	Doxorubicin, Bleomycin, Vinblastine (30-36 weeks)
9	HL	13	ABVD (15-35 weeks and in puerperium)
10	Bone metastasis in breast cancer	15	Docetaxel (19-31 weeks and in puerperium)
11	Ovarian cancer	17	Surgery (23 weeks)
12	AML	17	Daunorubicin, Ara-C (17 weeks)
13	Breast cancer	18	Surgery (19) + Adriblastine (in puerperium)
14	NHL	20	Clorambucil (20-24 weeks)
15	AML	21	Idarubicin, ATRA (21-25 weeks)
16	Jaw cancer	23	TPN, Surgery (23 weeks) + Rt (26-37 weeks)
17	Ovarian cancer	24	Delayed treatment after delivery
18	HL	24	ABVD (24-27 weeks and in puerperium)
19	HL	24	ABVD (24-26 weeks), + Rt (in puerperium)
20	NHL	24	Doxorubicin, CF, Etoposide, Ara-C, Bleomycin, Vincristine (24-37 weeks)
21	Ovarian cancer	25	Surgery (26 weeks)
22	Melanoma	25	aINF (26-30 weeks)
23	Astrocytoma recurrence+	26	Surgery (26 weeks)
24	Bone metastasis in breast cancer	26	Surgery (26 weeks) + Epirubicin, Taxotere and Rt (in puerperium)
25	Cervical cancer	27	Delayed treatment after delivery
26	Sigmoid colon cancer	28	Surgery (29 weeks)
27	AML	28	Daunorubicin, Ara-C (28 weeks)
28	Gastric cancer+	28	TPN, delayed treatment after delivery
29	Sigmoid colon cancer+	30	TPN, delayed treatment after delivery
30	NHL	30	Epirubicin, CF, Etoposide, Ara-C, Bleomycin, Vincristine (34-37 weeks)
31	Breast cancer	32	Delayed treatment after delivery
32	Breast cancer	37	Delayed treatment after delivery

CML, chronic myeloid leukemia; IFN, interferon; Rt, radiotherapy; AC, Adriamycin+Cyclophosphamide; LEEP, loop electrosurgical excision procedure; TPN, total parenteral nutrition; HL, Hodgkin's lymphoma; ABVD, Adriamycin+Bleomycin+Vinblastine+Dacarbazine; Ara-C, Cytosine-Arabinoside; NHL, non-Hodgkin's lymphoma; AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; CF, Cyclophosphamide; +Maternal death.

mean birth weight and percentile (according to a national standard curve) were 2051 g ±677 and 41±24, respectively. There were no cases of spontaneous abortions or intrauterine foetal death. The rate of foetal abnormalities was 9% (three cases). Diaphragmatic hernia occurred in an infant born to a patient treated with radiotherapy between 10 and 17 weeks. The baby was born alive, but he died shortly after delivery because of this congenital malformation. Hypoacusia occurred in a premature infant, born at 33 weeks of gestation to a patient treated with radiotherapy between 24 and 33 weeks; hypospadia occurred in an infant born to a patient treated with chemotherapy started at 28 weeks.

All the other infants at discharge were physically and neurologically normal. Maternal and infant follow-ups were carried out for 1 year after delivery.

Discussion

The occurrence of malignancies during pregnancy has increased over the past decades. The optimal course is often a dilemma both for the pregnant patient and her physician. Since it is impossible to design prospective randomised clinical trials in this field, relevant data have been generated from case reports and matched historical cohort studies in order to evaluate the treatment

Table II. *Pregnancy outcome in our series of patients.*

Case	Week of delivery	Mode of delivery	Birth weight (g)	Birth weight percentile	Apgar score	Neonatal outcome
1	36	CS	2390	24	8-9	Healthy child
			2250	15	8-9	Healthy child
2	40	CS	2800	15	INT	Diaphragmatic hernia,†
3	36	VD	3120	81	9-9	Healthy child
4	38	VD	3150	59	9-10	Healthy child
5	30	VD	1620	83	8-9	Healthy child
6	29	CS	1580	79	8-8	Healthy child
7	33	CS	1830	24	8-9	Hypoacusia
8	36	CS	2650	41	8-9	Healthy child
9	36	VD	2190	12	6-9	Healthy child
10	32	CS	1620	23	8-9	Healthy child
11	35	CS	2640	54	8-9	Healthy child
12	28	CS	1370	79	INT	Healthy child
13	33	CS	2560	42	8-9	Healthy child
14	39	CS	3020	39	9-9	Healthy child
15	34	CS	1950	19	8-9	Healthy child
16	38	VD	3100	54	9-10	Healthy child
17	32	CS	1330	15	8-8	Healthy child
18	37	CS	2850	45	8-8	Healthy child
19	37	CS	2450	17	9-9	Healthy child
20	35	CS	1980	10	8-9	Healthy child
21	30	CS	1380	34	INT	Healthy child
22	30	CS	1630	62	7-7	Healthy child
23	31	CS	900	8	INT	Healthy child
24	28	CS	1275	69	INT	Healthy child
25	27	CS	1000	59	INT	Healthy child
26	31	CS	1695	45	8-8	Healthy child
27	28	CS	1150	55	INT	Hypospadia, RDS
28	28	VD	1170	31	7-8	Healthy child
29	34	CS	1980	21	7-7	Healthy child
30	36	VD	3020	76	9-9	Healthy child
31	34	VD	2400	49	9-9	Healthy child
32	38	CS	2720	25	INT-8	Healthy child

CS, caesarean section; VD, vaginal delivery; INT, intubation; IVH, intraventricular haemorrhage; HMP, hyaline membrane pneumonia; RDS, respiratory distress syndrome; † , neonatal death.

outcomes and issues concerning the management of malignancy.

Both maternal and foetal well-being should be considered when therapy is planned during pregnancy. One of the major problems is the timing of therapeutic interventions with regard to foetal development or toxicity.

In the early stage of pregnancy, the diagnosis of malignancy poses different questions regarding the best treatment and foetal prognosis. In the late stage of pregnancy, treatment can be performed during pregnancy or partially in pregnancy and puerperium. In some cases, treatment is completely delayed until after delivery.

In the management of pregnant patients with cancer, potential issues related to ethical and non-ethical concerns are raised. The discovery of cancer in pregnancy requires a collaborative and multidisciplinary team, including specialists in obstetrics, surgery, oncology, radiotherapy, neonatology, psychology and, sometimes, an intervention of an expert in bioethics. Optimal maternal treatment has always to be balanced against foetal well-being. The patient can analyse the eventual risks and the benefits of the treatment choice and treatment can be planned accordingly.

In our experience, after accurate counselling, every woman weighed the different therapeutic options, namely undergoing appropriate therapy during pregnancy, delaying therapy until after delivery (when possible), or aborting voluntarily.

When the diagnosis of cancer is made in the first trimester, immediate treatment is necessary only when the woman's life is in serious danger. Surgery is generally performed in the second trimester, which is the safest time to avoid miscarriage and the onset of labour (17-20).

In this series, in the two cases of cervical cancer, diagnosis was made in the first trimester, while surgical treatment was performed in the second to avoid the above-mentioned risks.

In all three cases complicated by cervical cancer, a premature delivery occurred. In the first case (n=5), vaginal delivery occured at 30 weeks due to cervical incompetence, probably induced by the conization performed two weeks earlier. In the second case (n=6), a caesarean section was performed because of the onset of preterm labour with breech presentation. Finally, in the last case (n=25) a premature caesarean section was planned because of the diagnosis of advanced disease.

In the first trimester, radiotherapy was used in a case of astrocytoma by supra-diaphragmatic irradiation. When supra-diaphragmatic irradiation is given, the foetus receives low radiation exposure. On the contrary, as the foetus grows, its exposure to supra-diaphragmatic radiation increases. Such radiation may not be appropriate in the more advanced stages of pregnancy (21).

When malignancy was diagnosed in the second trimester, surgery and chemotherapy were employed according to each case and the timing of delivery was planned at a gestational age compatible with the survival of the infant.

When malignancy occurred in the third trimester, the decision to delay treatment until after delivery was the preference (63%). This choice allows the possibility of reaching infant viability, without compromising maternal health. Therefore, a premature delivery by caesarean section is usually planned in order to treat the mother as soon as possible. Since there is a strong possibility of preterm birth, induction of foetal lung maturity by prenatal administration of steroids (betametasone 12 mg/day for 2 days) is indicated. Although the infants are faced with the risks of a premature birth, they are not subjected to the effects of the maternal treatment.

When the pregnant patients were treated with chemotherapy, the delivery was planned after an interval period to reduce maternal and neonatal toxicity. In general, delivery should be avoided during the maternal toxic nadir period, 2-3 weeks after treatment. The delay of delivery after chemotherapy allows for foetal drug excretion. Chemotherapy administered shortly before delivery might be eliminated from the foetus. Drugs might, therefore, persist in the newborn, especially true for preterm infants who have a limited ability to metabolise drugs, because of immature liver and kidneys (22).

When the pregnant patients were affected by malnutrition or inadequate oral intake, they were supported by total parenteral nutrition, which provided nutritional support for the mothers and was vital to sustain and ameliorate foetal growth, as demonstrated by our previous report (15). Thanks to the improved maternal conditions and increased foetal growth, viable infants may be delivered even in such complicated pregnancies that might otherwise be terminated by naturally occurring events.

In the present series, a good pregnancy outcome was generally observed, even if many preterm deliveries were encountered (82%). The preterm delivery was generally planned according to different parameters, such as disease progression, maternal schedule treatment and foetal risks. The rate of malformations was 9%, which is higher than the rate of 3-5% in the general population. In our opinion, maternal radiotherapy could be responsible for the case of congenital diaphragmatic hernia, although the case of hypoacusia was probably not the result of preterm delivery or maternal treatment. In the case of hypospadia, the mother did not receive any treatment during embryogenesis because of cancer diagnosis.

The rate of low-birth-weight infants (<2500 g) was much higher (67%) than that of the general population (6-12%) (23), due to the necessity to anticipate delivery because of advanced disease and to chemotherapy use, as shown in a recent review (24). Another cause of this condition was severe maternal undernutrition. In some cases, it was mandatory to recourse to total parenteral nutrition to ameliorate the maternal nutritional status and, therefore, foetal well-being (15). Moreover, in a recent review it was stressed that in non-obstetric surgery, general anaesthesia, longer surgery time and intra-abdominal procedures are all associated with lower birth weights (25). Different factors combined with the decision to induce premature delivery can contribute to high rate of low-birth-weight infants.

It is reported that pregnant women with cancer are often diagnosed at a later stage compared to non-pregnant women (26). Although cancer may be diagnosed at a more advanced stage, pregnant patients with a diagnosis of cancer do not appear to have a more aggressive clinical course.

Conclusion

It is mandatory to treat every curable malignant disease in pregnant women and to plan delivery after considering the effects of the treatment on both the mother and the foetus.

The presence of cancer in pregnancy requires a multidisciplinary team of experts who can offer the best care to the mother and foetus. Moreover, the high rate of preterm births and low-birth-weight infants (<2500 g) delivered by mothers with cancer indicates that these pregnancies should be followed in a tertiary centre equipped with a neonatal intensive care unit that can guarantee accurate treatment.

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Received January 23, 2006
Accepted February 27, 2006