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ORIGINAL ARTICLE

A Japanese survey of malignant disease in pregnancy

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Abstract

Background In recent years, the incidence of malignant disease in pregnancy has been increasing, but there are few large-scale surveys of malignant disease in pregnancy in Japan. The aim of this study was to survey malignant disease occurring during pregnancy in Japan.

Methods Malignant disease in pregnancy was defined as diagnosis or treatment for malignant disease, except in situ carcinoma during pregnancy, or within 1-year postpartum. First, a primary survey questionnaire of the incidence of malignant disease in pregnancy and the number of deliveries over the course of 2014 was sent to 510 medical centers in Japan. Second, the survey questionnaires on the incidence of malignant diseases in pregnancy were collected and analyzed in detail.

Results Of the 510 medical centers, 411 (81%) responded to the survey. There were 215,372 deliveries and 189 incidents (0.09%) of malignant disease in pregnancy. Of the 189 patients with malignancy, 157 detailed responses about the patients were received. The most frequently encountered cancer types were cervical cancer (36%), breast cancer (24%), and ovarian cancer (15%). During the 2 years after delivery, 15 patients (1 with breast cancer, 2 with ovarian cancer, 3 with hematologic malignancy, 4 with intestinal cancer, and 5 with others) died of the disease; most of them had advanced disease. In particular, 88% of the patients with intestinal cancers at diagnosis had advanced disease, and half of them died of disease.

Conclusions In Japan, the most common malignancies in pregnancy in order of frequency are cervical cancer, breast cancer, and ovarian cancer. Early diagnosis and appropriate management of cancer during pregnancy are important for improving maternal and neonatal outcomes, because advanced diseases have a poor prognosis.

Keywords Pregnancy · Cancer · Chemotherapy · Surgery

Introduction

In recent years, the incidence of malignant disease in pregnancy has been increasing due to the rising age of the mothers at pregnancy and the prevalence of malignant disease in young patients. The incidence of malignant disease in pregnancy is estimated to be 0.3–1.0 per 1000 deliveries [1–3]. Smith et al. examined the incidence of malignant disease during pregnancy or in the subsequent 12 months in more than 4.8 million deliveries in California over a 9-year period [1]. In their review, breast cancer was the most common malignancy, followed by thyroid cancer, and then cervical cancer in third place. In general, the most common malignancy in pregnancy is breast cancer. In Korea, Shim reported that breast cancer was the most common malignancy during pregnancy [4]. In the USA and European countries, melanoma during pregnancy is more common [5], but the incidence of melanoma in Korea is less than that in other countries. However, there are no large-scale surveys concerning the incidence of malignant disease in pregnancy in Japan.

In the management of pregnant women with malignant disease, there are two major problems: the mother and the fetus. The management of the infant has progressed well, especially in Japan, because if the fetus is delivered at greater than 28 week gestation, the intact survival rate is very high

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[6–8]. Although the pregnant woman with malignant disease should be treated as soon as possible, it is necessary to consider the life of the fetus as well. Recent strategies have been developed that allow the mother with cancer to be treated by surgery or chemotherapy with the fetus in utero [9–13]. However, complete data regarding pregnant patients with malignant disease are few. The aim of this study was to collect and analyze data concerning malignant disease in pregnancy in Japan. Accordingly, a nationwide survey was conducted, and its findings are reported.

Materials and methods

Malignant disease in pregnancy was defined the diagnosis or treatment of malignant disease, except in situ carcinoma, during pregnancy or within 1-year postpartum. If the patient was diagnosed as pregnant during the treatment for malignant disease or within 1 year after completion of the treatment for a malignant disease, such a case was included as malignant disease in pregnancy. First, a primary survey questionnaire of the incidence of malignant disease in pregnancy and the number of deliveries over the course of 2014 was sent to 510 medical centers, which consisted of perinatal medical centers or designated cancer hospitals. In Japan, most pregnant women with malignant disease were treated at perinatal medical centers or designated cancer hospitals. Therefore, it could be assumed that all pregnant women with malignancies were treated in the 510 medical centers in Japan.

Second, the cases of malignant disease in pregnancy were retrospectively gathered from each hospital and analyzed in detail. The following patients' data were collected: patient age, tumor type, histology, stage, treatment modality during pregnancy, outcome (within 2 years after delivery), gestational age at diagnosis, and delivery type. Fetal characteristics were also recorded, including age at delivery, birth weight, congenital anomalies, and Apgar scores. Elective abortion was defined as the termination of pregnancy before the 22nd week of gestation. The studies and data collected were all approved by each hospital's IRB. All data were collected in our data center and processed using Microsoft Excel 2010. The Chi squared test or Fisher's exact test was used for the analyses. Results were considered significant at $p < 0.05$.

Results

First, the primary survey received responses from 411 (81%) of 510 medical centers; there were 207,750 deliveries and 189 (0.09%) cases of malignant disease in pregnancy in the responding institutions. The government reported that Japan had 1,003,539 deliveries in 2014.

The detailed data of 157 (83%) of 189 cases were obtained. Of the 157 cases, 9 were diagnosed in pre-pregnancy, 130 during pregnancy, and 18 in the postpartum period. There were 56 patients with cervical cancer, 37 with breast cancer, 24 with ovarian cancer, 15 with hematologic malignancy, 8 (3 gastric cancer and 5 colon cancer) with gastrointestinal cancer, 6 with thyroid cancer, 4 with hepatobiliary pancreatic malignancy, 3 with tongue cancer, 1 with malignant brain disease, 1 with lung cancer, 1 with osteosarcoma, and 1 with bladder cancer (Fig. 1).

Patients' characteristics, treatments, and outcomes are shown in Table 1. As for the average age, hematologic malignancies were the youngest, but there was no significant difference in age among the tumor types. In advanced cases with more than stage III disease, there were no patients with cervical cancer, 10 (28%) with breast cancer, 5 (22%) with

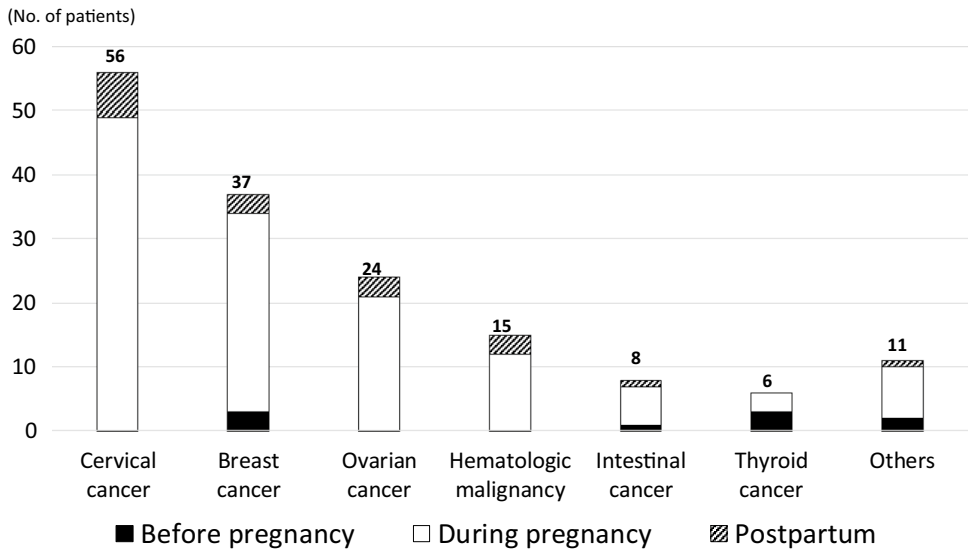

Fig. 1 Time of diagnosis of malignant disease in relation to pregnancy. Of the 157 cases, 9 were diagnosed in pre-pregnancy, 130 during pregnancy, and 18 in the postpartum period

Table 1 Characteristics, treatments, and outcomes

	Cervical cancer ($N=56$)	Breast cancer ($N=37$)	Ovarian cancer ($N=24$)	Hematologic malignancy ($N=15$)	Intestinal cancer ($N=8$)	Thyroid cancer ($N=6$)	Others ($N=11$)
Median age, years (range)	34 (25–42)	35 (27–41)	32 (19–41)	29 (25–37)	35 (29–40)	31 (23–35)	34 (28–41)
Stage							
I	51 (91%)	8 (22%)	16 (64%)	N/A		1 (17%)	2 (18%)
II	4 (7%)	13 (36%)	1 (4%)	N/A	1 (13%)	1 (17%)	
III		5 (14%)	2 (8%)	N/A	1 (13%)		2 (18%)
IV		3 (8%)	1 (4%)	N/A	6 (75%)		2 (18%)
Recurrence	2 (6%)	2 (8%)	N/A			1 (9%)	
Unknown	1 (2%)	6 (16%)	2 (8%)	N/A		4 (67%)	4 (36%)
During pregnancy							
Surgery	28 (50%)	19 (51%)	11 (46%)		2 (25%)	1 (17%)	2 (18%)
Chemotherapy	5 (9%)	11 (30%)	1 (4%)	5 (33%)			
Outcome							
NED	51 (91%)	28 (76%)	19 (79%)	7 (47%)	3 (38%)	6 (100%)	3 (27%)
AWD	2 (4%)	6 (16%)	2 (8%)	3 (20%)			1 (9%)
DOD		1 (3%)	2 (8%)	3 (20%)	4 (50%)		5 (45%)
Unknown	3 (5%)	2 (5%)	1 (4%)	2 (13%)	1 (13%)		2 (18%)

N/A not applicable, *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease

ovarian cancer, 7 (88%) with intestinal cancer, and one each of lung cancer, osteosarcoma and bladder cancer.

There were 63 surgeries during pregnancy (24 with conization, 4 with trachelectomy, 19 with mastectomy, 11 with oophorectomy, and 5 with other surgeries). In the colon cancer patient who had ileocecal resection at 21 weeks of gestation, the delivery was performed at 22 weeks, but the relationship between the surgery and preterm delivery is unclear. The remaining surgical management during pregnancy had no negative impact on the pregnancy. Chemotherapy during pregnancy was performed in 22 cases (11 with breast cancer, 5 with cervical cancer, 5 with hematologic malignancies, and 1 with ovarian cancer). There were no reported cases of congenital malformations or death of the fetus due to the exposure to chemotherapy However, three pregnant patients who had chemotherapy for leukemia had preterm deliveries at 24, 25, and 26 weeks of gestation, and it is unclear if there was a relationship between preterm delivery and treatment.

Eleven patients were lost to follow-up after delivery. Fifteen patients died of the disease within 2 years after delivery, and the total mortality rate was 9.6%. These 15 patients are shown in Table 2. Most of these patients had advanced disease and a short interval between diagnosis and delivery.

Obstetric outcomes are shown in Table 3. The median gestational age at the time of diagnosis was 20 weeks. The latest diagnostic age was for hematologic malignancies at 28 weeks. Of 157 patients, 80 (51%) had full-term births, and 56 (37%) had preterm births. The median gestational age at delivery in the patients with breast, ovary, and thyroid cancers was full term, but the remaining patients with cervix, hematological, and gastrointestinal malignancies had an average delivery time that was preterm. Ten cases had delivery during 22–27 weeks, 46 during 28–35 weeks, and 80 at more than 36 weeks of gestation. The rate of preterm delivery was 41%. All infants born preterm were treated in neonatal intensive care units. Of 80 infants delivered at full term, only two were treated in neonatal intensive care units. The patients with cervical cancer had the highest incidence of cesarean section compared to patients with other cancers ($p<0.001$).

One patient had a spontaneous abortion, and 20 (13%) patients selected to terminate their pregnancies due to the cancer; 9 patients were diagnosed during the first trimester, and 11 were diagnosed during the second trimester. In the 10 patients with cervical cancer, 9 were immediately treated with radical hysterectomy after termination of pregnancy, and the remaining patient was treated with chemoradiotherapy following termination of pregnancy. Eight patients (1 with breast cancer, 2 with ovarian cancers, 3 with intestinal cancers, 1 with lung cancer, and 1 with malignant brain disease) were treated with surgery, and the remaining 2 patients with hematologic malignancies were treated with chemotherapy after termination of pregnancy.

Table 2 Patients who died of disease

	Tumor type	Stage	Age (years)	GA at diagnosis (weeks)	GA at delivery (weeks)	Type of delivery	Treatment	Period from delivery (months)
1.	Breast	IV	30	27	32	Cesarean	Surgery + chemotherapy	7
2.	Ovary	IIIC	32	28	28	Cesarean	Surgery + chemotherapy	17
3.	Ovary	Recurrence	29	33	35	Cesarean	Surgery + chemotherapy	8
4.	Leukemia (AML)	N/A	25	31	31	Cesarean	Chemotherapy	23
5.	Leukemia (ATL)	N/A	30	12	15	E-abortion	Chemotherapy	15
6.	Non-Hodgkin (DLBCL)	N/A	36	2 weeks after delivery	36	Vaginal	Chemotherapy	11
7.	Gastric	IV	32	34	34	Cesarean	None	1
8.	Gastric	IV	29	18	18	E-abortion	Chemotherapy	5
9.	Colon	IV	37	2 weeks after delivery	39	Vaginal	Chemotherapy	7
10.	Appendix	IV	33	35	35	Cesarean	Surgery + chemotherapy	6
11.	Liver	IV	38	16	20	E-abortion	Surgery + chemotherapy	7
12.	Ductal	IV	33	8 weeks after delivery	34	Cesarean	Chemotherapy	21
13.	Pancreas	IV	34	20	25	Cesarean	Chemotherapy	13
14.	Osteosarcoma	N/A	36	40	40	Cesarean	Chemotherapy	6
15.	Brain	N/A	32	23	29	Cesarean	None	1

AML acute myeloid leukemia, *ATL* adult T-cell leukemia, *DLBCL* diffuse large B-cell lymphoma, *E-abortion* elective abortion, *GA* gestational age, *N/A* not applicable

Table 3 Neonatal outcomes

	Cervical cancer ($N=56$)	Breast cancer ($N=37$)	Ovarian cancer ($N=24$)	Hematologic malignancy ($N=15$)	Intestinal cancer ($N=8$)	Thyroid cancer ($N=6$)	Others ($N=11$)
GA (median) at diagnosis							
Weeks (range)	17 (5–34)	19 (4–34)	18 (7–38)	28 (12–35)	20 (4–35)	16 (4–37)	23 (10–40)
Delivery							
Full term delivery	20 (36%)	27 (73%)	18 (75%)	4 (27%)	2 (25%)	6 (100%)	3 (27%)
Preterm delivery	25 (45%)	9 (24%)	4 (16%)	9 (60%)	3 (38%)		6 (56%)
Elective abortion	10 (18%)	1 (3%)	2 (8%)	2 (13%)	3 (38%)		2 (18%)
Spontaneous abortion	1 (2%)						
GA (median) at delivery							
Weeks	34	37	37	34	33	38	34
Mode of delivery							
Vaginal delivery	9 (20%)	20 (56%)	9 (75%)	9 (69%)	3 (60%)	4 (67%)	2 (22%)
Cesarean section	36 (80%)	16 (44%)	13 (25%)	4 (31%)	2 (40%)	2 (33%)	7 (78%)

GA gestational age

Discussion

In the primary survey, 411 (81%) of 510 medical centers responded and reported that there were 207,750 deliveries and 189 (0.09%) incidents of malignant disease in pregnancy. In 2014, Japan had one million deliveries, and this survey covered 21% of the total deliveries. However, most patients with malignant disease in pregnancy were treated at perinatal medical centers or designated cancer hospitals in Japan. In this survey, the reply rate from the hospitals was 81%. Therefore, this survey could be seen as an assessment of malignant disease in pregnancy from about 810,000 deliveries. Therefore, it can be suspected that the incidence of malignant disease in pregnancy in Japan is about 0.2 per 1000 normal deliveries, since there was 189 cases of malignant diseases among the pregnancies in this survey. In general, the reported incidence of malignant disease in pregnancy was 0.3–1.0 per 1000 deliveries in the world [1–3]. The incidence of malignant disease in pregnancy in Japan might be slightly lower than in other countries.

In Japan, cervical cancer is the most common malignant disease in pregnancy, whereas in the US, breast cancer is the most common [1]. It seems that there is a difference in the distribution of malignant disease in pregnancy in each country. In the future, cervical cancer is expected to decrease in developed countries due to the global distribution of HPV vaccination. However, Japan has a low prevalence of vaccination [14–16]. Furthermore, acceptance of cervical cancer screening via the Pap test is very low in young adult Japanese women [17]. The age at delivery is rising in Japan, and the average age at delivery is more than 30 years. We wonder if the risk of future cervical cancer during pregnancy will increase due to the low HPV vaccination rate, the low Pap test rate, and the increasing of late age at pregnancy.

Twenty patients (13%) decided to terminate their pregnancies due to the cancer. In such cases, cervical cancer was the reason for selecting termination of pregnancy, because the treatment for cervical cancer directly affects the fetus. However, there were 4 cases of trachelectomy and 5 of chemotherapy during pregnancy reported in the present survey. If the patient was diagnosed with cervical cancer in stage 1B1 with tumor size larger than 2 cm, or in 1B2 with negative pelvic lymph nodes during the second trimester of pregnancy, the European Society of Gynecological Oncology (ESGO) guidelines recommend that neoadjuvant chemotherapy should be performed until fetal maturity [9, 10, 18]. The use of chemotherapy up to fetal maturity during pregnancy might increase in the future in Japan.

When a pregnant woman was diagnosed as having cancer, safe use of chemotherapy during the second and third trimesters of pregnancy has been reported, and pregnant women with cancer can accept therapy without definite neonatal harm [9–13]. In the present survey, such a strategy was adopted for cervical cancer, breast cancer, ovarian cancer, and hematologic malignancies. Recently, some authors reported that chemotherapy during pregnancy for colorectal cancer might be expected to result in delayed child-bearing [19]. If such a strategy is to be used, two things are needed, efficacy for malignancies and safety for the fetus. In the first trimester, chemotherapy should not be given because of the increased risk of spontaneous abortion and the effects on organogenesis. Chemotherapy regimens should be given to patients in the second or third trimester of pregnancy. The commonly used chemotherapy regimen for gynecologic malignancies is carboplatin and paclitaxel. Carboplatin, paclitaxel, and antibiotic agents (eg, doxorubicin) have the lowest associated risks [3, 20, 21]. Alkylating agents (eg, cyclophosphamide) and antimetabolites (eg, methotrexate) are reported to have the greatest risk for adverse pregnancy outcomes, especially first-trimester malformations [20, 21].

In the present survey, three patients who underwent chemotherapy for leukemia had preterm deliveries, but the interaction between chemotherapy and preterm delivery was unknown. However, de Hann reported that babies exposed to antenatal chemotherapy might be more likely to be small for gestational age and require NICU admission than babies not so exposed [14]. Furthermore, the possible adverse effects of chemotherapy on the developing brain of the fetus have not been resolved, and data are limited to retrospective cases. Therefore, more such data need to be collected worldwide.

There was a difference in stage at the diagnosis of malignancy among tumor types. There were no patients with advanced cervical cancer in the present survey, but 28% of the patients with breast cancer had advanced disease. Cervical cancer is easily detected, because visual inspection is routine in prenatal care. In contrast, it is difficult to detect breast cancer during pregnancy due to breast enlargement during pregnancy. The diagnosis of malignancy during pregnancy is sometimes delayed because of the changes in pregnant women due to hormonal changes. The diagnosis of intestinal cancer during pregnancy is sometimes delayed, because radiologic examination is not recommended due to the risk for the fetus. In the present survey, 88% of the patients with intestinal cancer had advanced disease at diagnosis. If a pregnant woman has long-term complaints of abdominal pain or discomfort, endoscopy should be performed.

In Japan, the most common malignancies in pregnancy are cervical cancer, breast cancer, and ovarian cancer, in order of frequency. In the present survey, no pregnant patients had melanoma. Thus, there appears to be a difference in the distribution of the types of malignant disease

during pregnancy by race or country. There were no cases of advanced disease in the patients with cervical cancer, and the incidences of advanced breast cancer (28%) and ovarian cancer (22%) were lower than of advanced intestinal cancer (88%) during pregnancy. Fifteen patients with malignant disease during pregnancy died of disease within 2 years after delivery, and most these patients had advanced disease. In particular, 88% of the patients with intestinal cancer had advanced disease, and half of the patients with intestinal cancer died of disease. Early diagnosis and appropriate management of cancer during pregnancy are important for improving maternal and neonatal outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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