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Birth Outcomes of Anticancer Drug Prescriptions during Pregnancy: A Case Series from a Japanese Claims Database

Kentaro Tajima [1], Tomofumi Ishikawa [1], Masami Tsuchiya [1,2], Masafumi Kikuchi [3,4], Taku Obara [4,5,6,*] and Nariyasu Mano [1,4]

1 Laboratory of Biomolecule and Pathophysiological Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8574, Japan
2 Department of Pharmacy, Miyagi Cancer Center, Natori 981-1293, Japan
3 Pharmacy Education and Research Center, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan
4 Department of Pharmaceutical Sciences, Tohoku University Hospital, Sendai 980-8574, Japan
5 Division of Preventive Medicine and Epidemiology, Tohoku University Tohoku Medical Megabank Organization, Sendai 980-8573, Japan
6 Department of Molecular Epidemiology, Environment and Genome Research Center, Graduate School of Medicine, Tohoku University, Sendai 980-8573, Japan
* Correspondence: obara-t@hosp.tohoku.ac.jp; Tel.: +81-22-717-7528

Abstract: We aimed to evaluate the adverse birth outcomes of anticancer drug prescription during pregnancy using a Japanese claims database from 2005 to 2019. We applied validated claims-based algorithms to identify pregnant women with birth outcomes, and evaluated drug prescription during pregnancy. The causal relationship between anticancer drugs and adverse birth outcomes was evaluated using the Council for International Organizations of Medical Sciences Working Group VI criteria. Thirteen women with anticancer drugs prescription during pregnancy were identified (mean age: 34.6 years). Atrial/ventricular septal defect was observed in one infant after exposure to cyclophosphamide and doxorubicin for breast cancer in the second and third trimesters. One woman on several anticancer drugs (cyclophosphamide, cytarabine, daunorubicin, l-asparaginase, methotrexate, nelarabine, and vincristine) for acute lymphoblastic leukemia, one on imatinib for chronic myeloid leukemia, and one on cisplatin and fluorouracil for cervical cancer had miscarriages after exposure in the first trimester. A relationship between those anticancer drugs and miscarriage could not be ruled out, while no relationship was identified regarding the atrial/ventricular septal defect considering the period of exposure and organogenesis. Our results suggest increased risk of miscarriage with the use of several anticancer drugs such as methotrexate, imatinib, cisplatin, and fluorouracil in the first trimester.

Keywords: cancer; claims database; Japan; live birth; miscarriage

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1. Introduction

Cancer during pregnancy is reported in approximately one in 1000–5000 pregnant women in Western countries [1,2]. Although the epidemiological data on the incidence of cancer during pregnancy in Japan are unknown, cases are not common. Given the rising childbearing age among women [3], the number of pregnant women who are diagnosed with cancer and who require cancer treatment during pregnancy will increase [4].

Anticancer drug usage during pregnancy may elevate risks of miscarriage and congenital malformations of the fetus. However, the potential risk of adverse birth outcomes after taking specific anticancer drugs is limited in Japanese clinical guidelines except for cyclophosphamide and methotrexate in the first trimester and anti-human epidermal growth factor receptor type 2 and endocrine therapy in pregnancy [5–7]. Although case series and retrospective cohort studies of some anticancer drugs were conducted in Western

countries [8–14], few researchers examined the relationship between individual anticancer drugs and birth outcomes. Moreover, there have been no epidemiological studies except for case reports to evaluate birth outcomes after administration of anticancer drugs in Japan. Interventional studies to evaluate the exposure to anticancer drugs during pregnancy and subsequent birth outcomes are not feasible from ethical perspectives in general. Thus, observational studies to explore birth outcomes associated with specific anticancer drugs during pregnancy play an important role in decision-making between healthcare professionals and pregnant women with cancer. A claims database is a useful data source to capture a large population and eliminate recall bias which can be a concern in retrospective observational studies [15,16].

We aimed to evaluate the risk of adverse birth outcomes of anticancer drug prescriptions during pregnancy using a Japanese claims database.

2. Materials and Methods

2.1. Study Design and Data Source

We conducted a case series study by using a nationwide health insurance claims database provided by JMDC (Tokyo, Japan). This database is the largest commercially available insurance-based claims database in Japan [17], which has been utilized in various research of pregnant women [18–22]. It contains inpatient, outpatient, and pharmacy claims from health insurance societies in the form of structured data including demographic, International Classification of Diseases 10th revision (ICD-10), medical procedure, and medication information. Data standardization and record anonymization were performed [23].

This study was approved by the Institutional Review Board of Tohoku University School of Medicine on 22 June 2021 (receipt number: 2021-1-226). Informed consent was not required because this was an observational study with anonymized secondary data.

2.2. Eligible Study Population

From the claims data between January 2005 and November 2019, we selected women of reproductive age (from 15 to 49 years) [24]. To identify the women who were estimated to be pregnant and have birth outcomes, we applied the validated claims-based algorithms for pregnancy (combination algorithm with diagnosis, medical procedure, medication, and medical service addition) and birth outcomes (selected algorithm for live birth, miscarriage, induced abortion, and caesarean section) based on previous validation studies [25,26]. When multiple birth outcomes were identified in the same woman, only the initial outcome was used.

Subsequently, we identified women with anticancer drug prescription during pregnancy. The anticancer drugs were identified using the World Health Organization Anatomical Therapeutic Chemical code L01. The onset of pregnancy needs to be defined to evaluate the anticancer drug prescription during pregnancy; therefore, it was estimated by subtracting the gestational age recorded as a part of the diagnosis information in the claims [27]. If there were multiple diagnoses codes specifying the gestational age before the birth outcomes, the longest gestational age was used, as the gestational age in later stages of pregnancy is more accurate than that in early ones [28]. Women without data on gestational age in the diagnosis code, women without anticancer drug prescription between the estimated date of pregnancy onset and that of birth outcome, and women without a diagnosis code of cancer before the date of birth outcome were excluded. Anticancer drug prescriptions with ICD-10 codes (C00–C96) were used for the identification of cancer diagnoses, as the claims-based cancer diagnoses with anticancer drug prescription are accurate in general [29,30].

2.3. Data Analysis

The period of exposure to anticancer drugs was categorized into first trimester (pregnancy onset to week 13 day 6 of gestation), second trimester (week 14 day 0 to week 27 day 6

of gestation), and third trimester (later than week 28 day 0 of gestation) based on the estimated onset of pregnancy [28]. Regarding the date of medication, the dispensing date was used. If dispensing date was unavailable and we could confirm only the month of claims, we considered the date as the 15th day of the month of the claim. The days of supply for each oral anticancer drug were considered to estimate the timing of exposure and evaluate if they were within the period of pregnancy.

For the study population, data were collected on age, cancer, prescribed anticancer drugs and their exposure period, birth outcomes, days between pregnancy onset and birth outcome, concomitant treatment during pregnancy, and medical history including comorbidities. The outcome of live birth before 37 completed weeks of gestation was defined as preterm birth [31]. As for concomitant treatment, data were collected on drugs with a potential risk of fetotoxicity and congenital malformation which are defined by the clinical practice guidelines of the Japanese Society of Obstetrics and Gynecology and Japanese Association of Obstetrics and Gynecology [7], drugs with Food and Drug Administration pregnancy category D or X [32,33], and radiation exposure including computed tomography (CT) scan [34]. Additionally, the diagnosis of high-risk pregnancy which was defined by the Ministry of Health, Labour and Welfare was described as medical history, which has the potential of adverse birth outcomes including miscarriage [35].

For live birth outcomes, if the infants were enrolled with the same health insurer of the mothers during their birth month for over one year, we evaluated if the infants were born with congenital birth defects. The outcome of congenital malformation excluding chromosomal abnormalities (ICD-10: Q00-Q89) was assessed, as the validity of congenital malformation diagnoses claims in Japan had been examined in previous research [36].

Additionally, the causal relationship between anticancer drugs and adverse birth outcomes (miscarriage and congenital malformation) was evaluated by researchers referring to the criteria of "Evidence from Individual Cases" proposed by Council for International Organizations of Medical Sciences (CIOMS) Working Group VI [37]. Considering the characteristics of the outcomes and the evaluable information on claims data, the items 'positive rechallenge', 'positive dechallenge', 'corroboration of the accuracy of the case history', 'case clear-cut, easily evaluated', 'investigator's causality assessment', and 'lack of alternative explanation' were excluded from the assessment (Supplementary Table S1).

All analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

Of the 7,447,761 individuals included in JMDC Claims Database between January 2005 and November 2019, 303,512 women met the pregnancy algorithm, and 180,464 women met the algorithm for birth outcomes. Of these, the onset of pregnancy was estimated for 164,275 women. Of the 164,275 women, 1439 women were diagnosed with any cancer diseases before the date of birth outcome (Figure 1).

There were 3301 records of anticancer drug prescription for the 1439 women. The timing of exposure was evaluated in 3076 records (93.2%) based on dispensing date, and 15th day of the month of the claims was imputed for the other 225 records (6.8%) due to the lack of dispensing date. Finally, of 1439 women, 13 women with prescriptions of anticancer drugs during pregnancy were identified as the study population (Figure 1).

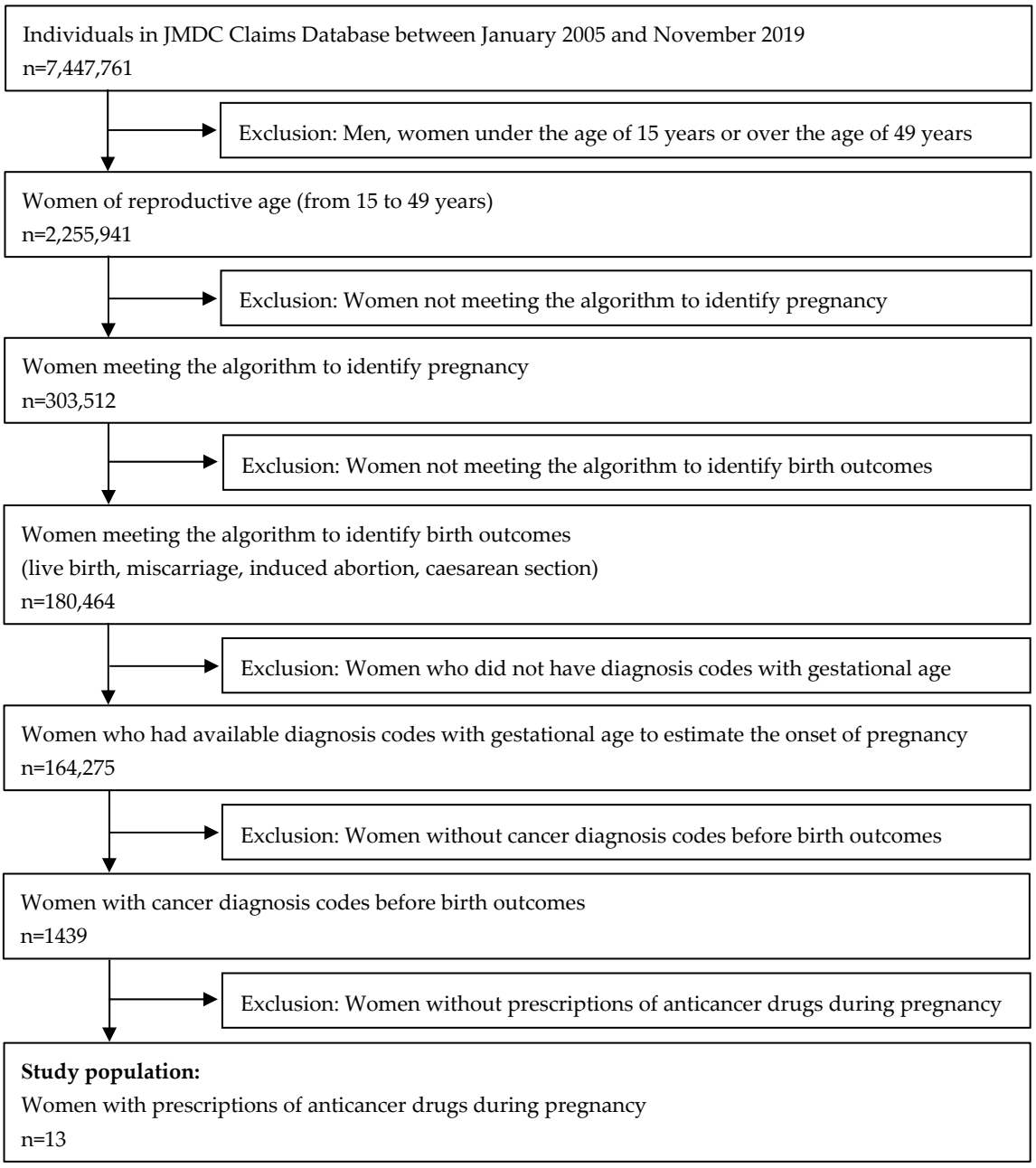

Figure 1. Selection of study population.

3.1. Description of the Study Population

The mean age was 34.6 (standard deviation: 5.0) years (Table 1). While various anticancer drugs were observed, cyclophosphamide (n = 5), doxorubicin (n = 4), and vincristine (n = 3) were frequently prescribed. The estimated number of anticancer drugs administered were six drugs in the first trimester, eight drugs in the second trimester, and seven drugs in the third trimester. Of the 13 women, 10 women had a live birth, and five women delivered by caesarean section. On the other hand, three women had miscarriages. The most frequently observed code of cancer diagnoses was leukemia (n = 5), but there were various diagnoses claim codes of other cancers too.

Table 1. Characteristics of study population (n = 13).

Age at the Time of Birth Outcomes, Year (Mean ± Standard Deviation)			**34.6 ± 5.0**
Anticancer drugs, n	Alkylating agent	Cyclophosphamide	5
		Dacarbazine	1
	Anticancer antibiotics	Doxorubicin	4
		Daunorubicin	2
		Bleomycin	1
	Vinca alkaloid	Vincristine	3
		Vinblastine	1
	Tyrosine kinase inhibitor	Imatinib	2
		Dasatinib	1
	Platinum	Carboplatin	2
		Cisplatin	1
	Antimetabolic agent	Cytarabine	1
		Fluorouracil	1
		Nelarabine	1
		Methotrexate	1
		Tegafur combination	1
	Taxane	Docetaxel	1
		Paclitaxel	1
	Monoclonal antibody	Rituximab	1
	Anticancer enzyme	L-asparaginase	1
Timing of anticancer medications, n	First trimester		6
	Second trimester		8
	Third trimester		7
Type of birth outcomes, n	Term live birth		3
	Preterm live birth		7
	Miscarriage		3
	Caesarean section		6
Types of cancers, n	Leukemia		5
	Breast cancer		2
	Cervical cancer		2
	Lymphoma		2
	Gastric cancer		1
	Ovarian cancer		1

The prescribed anticancer drugs and birth outcomes are summarized in Table 2. All women who had records of anticancer drug prescription in the second trimester and/or the third trimester had a live birth. However, one woman (No. 1) on cyclophosphamide, cytarabine, daunorubicin, l-asparaginase, methotrexate, and vincristine in the first trimester, one woman (No. 3) on imatinib in the first trimester, and one woman (No. 11) on cisplatin and fluorouracil in the first trimester had miscarriages. Among 10 live birth infants, five infants were enrolled with the same health insurer of the mothers during their birth month for over one year. Of these five infants, one infant (No. 7) had a diagnosis code of atrial/ventricular septal defect.

Table 2. Descriptions of prescribed anticancer drugs and birth outcomes (n = 13).

No	Age	Cancer	Anticancer Drugs	Exposure Timing	Birth Outcome	Days [a]	Other Prescriptions/ Medical Practice	Medical History
1	25	ALL	Cyclophosphamide Cytarabine Daunorubicin L-asparaginase Methotrexate Nelarabine Vincristine	T1 [b] T1 [b] T1 [b] T1 T1 [b] T1 T1 [b]	Miscarriage	65	Fluconazole (T1) [c] Gentamicin (T1) [d] Ketoprofen (T1) [d] Loxoprofen (T1) [c] CT scan (T1)	DIC, insomnia, sepsis, MDS
2	36	ALL	Cyclophosphamide Daunorubicin Vincristine	T2 T2 T2/T3	Preterm live birth by CS without CMs	224	Radiotherapy (T2)	DM, hypertension, threatened abortion, TPL, thrombocytopenia
3	42	CML	Imatinib [c]	T1	Miscarriage	48	Diclofenac (T1) [d] Ketoprofen (T1) [d]	Renal dysfunction, hypothyroidism, uterine fibroid, HF
4	34	CML	Imatinib [c]	T1 [b]	Term live birth	273	Naproxen (T1) [c]	TPL
5	40	CML	Dasatinib [c]	T1	Preterm live birth by CS [e]	238	Clindamycin (T1) [d] Loxoprofen (T1) [c]	Cervical cancer, threatened abortion, placenta previa with bleeding
6	36	Breast cancer	Cyclophosphamide Doxorubicin	T2/T3 T2/T3	Term live birth without CMs	266	Medroxyprogesterone (T1) [c]	Threatened abortion, TPL, haemorrhage in the third stage of labour
7	38	Breast cancer	Cyclophosphamide Doxorubicin	T2/T3 T2/T3	Preterm live birth by CS with atrial/ventricular septal defect	247	None	None
8	37	NHL	Cyclophosphamide Doxorubicin Rituximab Vincristine	T2/T3 [b] T2/T3 [b] T2/T3 [b] T2/T3 [b]	Term live birth by CS [e]	260	Etanercept (T1) Ketoprofen (T1/T3) [d] Ibuprofen (T2/T3) [c] Loxoprofen (T3) [c] CT scan (T2)	DM, RA, threatened abortion, hypothyroidism, abnormal uterine and vaginal bleeding

Table 2. *Cont.*

No	Age	Cancer	Anticancer Drugs	Exposure Timing	Birth Outcome	Days [a]	Other Prescriptions/ Medical Practice	Medical History
9	28	HL	Bleomycin Doxorubicin Dacarbazine Vinblastine	T2/T3 T2/T3 T2/T3 T2/T3	Preterm live birth by CS without CMs	231	Fluconazole (T3) [c]	DM, MI, CHF, insomnia, TPL, Amniotic infection
10	37	Cervical cancer	Carboplatin	T2/T3	Preterm live birth by CS [e]	233	Fradiomycin (T2) [d] Ibuprofen (T2) [d] CT scan (T2)	Threatened abortion
11	28	Cervical cancer	Cisplatin Fluorouracil	T1 T1	Miscarriage	56	Loxoprofen (T1) [c] Sodium valproate (T1) [c] CT scan (T1)	Epilepsy
12	32	Gastric cancer	Docetaxel Tegafur combination [c,f]	T2/T3 T2/T3	Preterm live birth without CMs	234	None	GAD, hypothyroidism, threatened abortion, TPL, arrhythmia
13	37	Ovarian cancer	Carboplatin Paclitaxel	T1 [b]/T2 T1/T2	Preterm live birth[e]	201	Ketoprofen (T1) [d] Loxoprofen (T1) [c] Diclofenac (T1/T2) [d] Betamethasone/gentamicin (T2) [d] CT scan (T1/T2)	Schizophrenia, depression, parkinson's disease, insomnia, autoimmune thyroiditis, asthma

Abbreviation: ALL, acute lymphoblastic leukemia; CHF, congestive heart failure; CML, chronic myeloid leukemia; CMs, congenital malformations; CS, caesarean section; CT, computed tomography; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; HF, heart failure; HL, Hodgkin's lymphoma; GAD, generalized anxiety disorder; MDS, myelodysplastic syndromes; MI, myocardial infarction; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; T1, first trimester; T2, second trimester; T3, third trimester; TPL; threatened preterm labor. [a] Days were defined as the number of days from the onset of pregnancy to the birth outcome. [b] The date of anticancer drug prescription was imputed as the 15 th day of the month of the claims for estimating the exposure timing. [c] Dosage form is oral. [d] Dosage form is topical. [e] Presence or absence of congenital malformations was not evaluable because the infants were not enrolled with the same health insurer of the mothers. [f] Tegafur combination was prescribed as tegafur/gimeracil/oteracil potassium.

3.2. Causal Assessments between Anticancer Drugs and Adverse Birth Outcomes

The assessment of the causal relationship between anticancer drugs and adverse birth outcomes is summarized in Table 3. The clinical course of these four cases is shown in Supplementary Figure S1.

Case No. 1 with acute lymphoblastic leukemia which led to a miscarriage had prescriptions of methotrexate, which is known for the risk of miscarriage [7,38,39]. In addition, cytarabine and daunorubicin have the potential of causing adverse birth outcomes including miscarriage [40], while other anticancer drugs prescribed to case No. 1 have no definitive risk of adverse birth outcomes. The timing of miscarriage, as well as the amount and duration of estimated exposure of each anticancer drug, were plausible. Alternatively, concurrent disease codes such as disseminated intravascular coagulation syndrome have been pointed out as risk factors for miscarriage. Other drugs (fluconazole, gentamicin, loxoprofen, ketoprofen) and CT scans, which may be associated with miscarriage and could be confounding factors, were also observed in that pregnancy. By an overall causal assessment, the relationship between methotrexate and miscarriage was suggested although the added adverse effects of other concomitant anticancer drugs could not be ruled out.

Case No. 3 with chronic myeloid leukemia which led to a miscarriage had prescriptions of imatinib, which has the potential for the risk of miscarriage and congenital malformation [41,42]. The timing of miscarriage, as well as the estimated amount and duration of exposure to imatinib, were plausible, while other topical medication (diclofenac, ketoprofen) and the advanced age might be confounding factors. As a whole, the relationship between imatinib and miscarriage could not be ruled out.

Case No. 7 with breast cancer which resulted in a live birth with atrial/ventricular septal defect had prescriptions of cyclophosphamide and doxorubicin. Based on the literature review on breast cancer patients with pregnancy, although these two drugs could be relatively safely used in the second or third trimester [5,8,43], the risk of adverse outcomes is not fully excluded. Notably, the timing of estimated exposure was out of the typical heart organogenesis window period (four to nine weeks of gestation) [8,44]; thus, the time to onset did not seem plausible. Taken together, it appears that there was no relationship between either anticancer drug and the atrial/ventricular septal defect of the infant.

Case No. 11 with cervical cancer which led to a miscarriage had prescriptions of cisplatin and fluorouracil with no definitive conclusion regarding the risk of birth outcomes. The timing of miscarriage, as well as the amount and duration of estimated exposure to both anticancer drugs, were plausible. However, there were concurrent disease codes for epilepsy and prescribed medications (loxoprofen, sodium valproate), which may have elevated the risk of miscarriage and could be confounding factors. By the overall assessment, the relationship between both anticancer drugs and miscarriage could not be ruled out.

Table 3. Assessment of the causal relationship between anticancer drugs and adverse birth outcomes based on the criteria proposed by CIOMS working group VI.

Items of 'Evidence from Individual Cases' Proposed by CIOMS Working Group VI		No. 1 (Miscarriage) Cyclophosphamide Cytarabine Daunorubicin l-Asparaginase Methotrexate Vincristine	No. 3 (Miscarriage) Imatinib	No. 7 (Atrial/Ventricular Septal Defect) Cyclophosphamide Doxorubicin	No. 11 (Miscarriage) Cisplatin Fluorouracil
2.	Definitive	Identified risk: Methotrexate [7,38,39] Potential risk: Cytarabine [40] Daunorubicin [40] Not definitive risk: cyclophosphamide l-asparaginase nelarabine vincristine	Potential risk: Imatinib [41,42]	Not definitive risk: cyclophosphamide doxorubicin	Not definitive risk: cisplatin fluorouracil
3.	Time to onset plausible	Plausible: 12 days after nelarabine; 16 days after l-asparaginase; 34 days after other drugs	Plausible: 44 days after imatinib	Not plausible: Both drugs prescribed from week 17 of gestation	Plausible: 11 days after both drugs
5.	Lack of confounding risk factors	Confounding risk factors: Diagnosis related with high-risk pregnancy (DIC, insomnia, sepsis, MDS); Medications (fluconazole, gentamicin, ketoprofen, loxoprofen); Radiation (CT scan)	Confounding risk factors: Medications (diclofenac, loxoprofen); Advanced age	Lack of confounding risk factors in this study	Confounding risk factors: Diagnosis related with high-risk pregnancy (epilepsy); Medications (loxoprofen, sodium valproate); Radiation (CT scan).
6.	Amount and duration of exposure consistent/plausible with cause and effect [(a)]	Consistent/plausible: cyclophosphamide (once: 500 mg 5 vials); cytarabine (twice: 20 mg 2 vials); daunorubicin (twice: 20 mg 4 vials); l-asparaginase (twice: 5000 K unit 2 vials); methotrexate (twice: 5 mg 3 vials); nelarabine (three times: 250 mg 11 vials); vincristine (twice: 1 mg 2 vials).	Consistent/plausible: Imatinib (once [(b)]: 400 mg 4 days, once: 400 mg 38 days, once: 400 mg 21 days).	Consistent/plausible: cyclophosphamide (five times: 500 mg 2 vials); doxorubicin (five times: 50 mg 2 vials).	Consistent/plausible: cisplatin (once: 50 mg 2 vials, 10 mg 2 vials); fluorouracil (four times: 250 mg 4 vials).
9.	Co-medication unlikely to play a role	Likely based on item #5: Medications, radiation exposure.	Likely based on item #5: Medications, radiation exposure.	Unlikely based on item #5	Likely based on item #5: Medications, radiation exposure.

Abbreviation: CIOMS, Council for International Organizations of Medical Sciences; CT, computed tomography; DIC, disseminated intravascular coagulation; MDS, myelodysplastic syndromes. [(a)] The prescription of anticancer drugs during pregnancy is described. [(b)] One prescription record of imatinib was identified before the pregnancy onset, and the exposure for 3 days was estimated based on the information of dispensing date plus the days of supply.

4. Discussion

This was the first study to investigate the risk of adverse birth outcomes of anticancer drug prescriptions during pregnancy using a large claims database in Japan. The value of this study is in adding evidence on birth outcomes of specific anticancer drugs prescribed during pregnancy by utilizing criteria proposed by CIOMS working group VI.

Of the 13 women identified, 10 women with prescriptions of anticancer drugs during pregnancy gave live births. According to clinical guidelines [5,7,44,45], anticancer medications in the first trimester should be avoided in principle. Among the 10 women with live births, while three women had prescriptions in the first trimester, anticancer drugs in the second and/or third trimester were prescribed to seven women, which was consistent with the guidelines. Although one woman gave a live birth with atrial/ventricular septal defect code under cyclophosphamide and doxorubicin, the prescription was in the week 17 of gestation. As the window of the heart organogenesis period is week four to week nine of gestation, we could not prove a causal relationship between both anticancer drugs and congenital malformation. Noteworthily, the baseline risk of congenital malformation is around 3–5%, and cyclophosphamide plus doxorubicin in the second or third trimester could be administered safely based on previous research although a long-term follow-up is required especially for cardiac toxicity of doxorubicin [5,7,46]. In addition, the frequency of live birth with caesarean section was relatively higher than that in the general Japanese population [47]. The caesarean section might be selected considering disease condition of cancers and treatment schedule.

Among the 13 women, three women had miscarriages. In the causal assessment, the relationship between anticancer drugs and miscarriage could not be ruled out in these women although possible confounding factors were present. Of note, the risk of miscarriage is definitive for methotrexate in the first trimester, as it is also used for induced abortion in Western countries [7,38,39]. Additionally, the risk of miscarriage can be elevated by cytarabine, daunorubicin, and imatinib [40–42]. Thus, these drugs (especially methotrexate) might plausibly be causative drugs of miscarriage. Although a woman on cisplatin in the first trimester gave a live birth by caesarean section and two women with fluorouracil in the first trimester had a miscarriage and live birth based on case reports [48,49], the risk of miscarriage of these two drugs is still unclear owing to the limited evidence.

As the incidence of cancer and anticancer treatment during pregnancy are rare, healthcare providers do not have enough experience in managing such patients [50]. In the future, more pregnant women would need cancer care, as the childbearing age increases. Additionally, with advances in therapy, managing pregnancy and treatments would become complicated, and the need for counselling for decision-making will increase. As large-scale intervention studies remain limited owing to condition rarity and ethical reasons, observational studies similar to our study would be useful in terms of feasibility and timeliness.

Several limitations of this study exist. First, using a claims database hindered the collection of information on the stage and severity of cancer and the intention of each anticancer drug prescription. Thus, we could not assess whether the anticancer drugs were utilized with the notice of pregnancy. In addition, information regarding some potential confounding factors of miscarriage including body mass index and smoking/alcohol consumption habit was not available. Second, the sensitivity of the algorithms to identify birth outcomes was unknown; therefore, we may have not been able to identify all birth outcomes. However, as the high positive predictive value of the algorithms was confirmed [25], the possibility of misclassification regarding birth outcomes was low in our study. Third, the actual administration of anticancer drugs was not evaluable although prescription could be captured. Nevertheless, most of the identified anticancer drugs were administered as intravenous injections rather than oral administration so that our results would be expected to indicate true exposure in general. Fourth, the actual dosages of each anticancer drug as well as the amount of placental transport were not evaluated, although we evaluated the amount of drug prescription. Fifth, this study design with limited sample size did not allow to compare the incidence rate of adverse birth outcomes of specific anticancer

drugs. It might be possible that restricting population with information of gestational age in the claims data would reduce the sample size. However, we believe our approach is appropriate under the current available data sources in Japan. JMDC claims database is one of the largest administrative databases in Japan and has a great advantage over hospital-based databases, as individuals can be followed even when they are transferred to another hospital unless they withdraw from the insurance society.

5. Conclusions

Despite the limited sample size, we suggest the potential risk of miscarriage of using several anticancer drugs such as methotrexate, imatinib, cisplatin, and fluorouracil in the first trimester. In addition to our observation, accumulating further evidence on the risk of adverse birth outcomes of anticancer drug usage during pregnancy is needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharma2010002/s1, Supplementary Table S1: Evidence from individual cases proposed by CIOMS working group VI and the investigated items in this study; Supplementary Figure S1. Clinical course of four cases with adverse birth outcomes.

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Institutional Review Board Statement: This study was approved by the Institutional Review Board of Tohoku University School of Medicine on 22 June 2021 (receipt number: 2021-1-226).

Informed Consent Statement: Informed consent was not required because this was an observational study with anonymized secondary data.

Data Availability Statement: The data that support the findings of this study are available from JMDC Inc. but were used under license for the current study; therefore, restrictions apply and the data are not publicly available.

Conflicts of Interest: K.T. and T.I. are employees of Pfizer and contributed to the present research independently of the company. N.M. received consultation fees from Daiichi Sankyo Co., Ltd. The other authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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