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Immune Checkpoint Inhibitor Use During Pregnancy and Outcomes in Pregnant Individuals and Newborns

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Abstract

IMPORTANCE With the widespread use of immune checkpoint inhibitors (ICIs), concerns about their pregnancy outcomes through maternal exposure have emerged, and clinical comparative data are lacking.

OBJECTIVE To assess the risk of pregnancy-, fetal-, and/or newborn-related adverse outcomes associated with exposure to ICIs compared with exposure to other anticancer agents.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, all reports mentioning a pregnancy-related condition and an antineoplastic agent (Anatomical Therapeutic Chemical classification group L01) used for a cancer indication registered in the World Health Organization international pharmacovigilance database VigiBase up to June 26, 2022, were extracted.

EXPOSURE Anticancer agents, including ICIs, used during pregnancy for a cancer indication. Immune checkpoint inhibitors included blockers of programmed cell death 1 (PD1) or its ligand (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA4).

MAIN OUTCOMES AND MEASURES The main outcome was the reporting odds ratio (ROR) for maternal, fetal, or newborn complications in patients treated with ICIs vs any other anticancer drug. Adverse events, categorized into 45 individual maternofetal adverse outcomes, were directly mapped to Medical Dictionary for Regulatory Activities preferred terms in VigiBase.

RESULTS A total of 3558 reports (ICI: 91 [2.6%]; other anticancer drugs: 3467 [97.4%]) were included in the analysis. In the ICI group, most reports were from the US (60 [65.9%]), and the mean (SD) patient age was 28.9 (10.2) years; in 24 of 55 reports with data on cancer type (43.6%), patients were treated for melanoma. The molecules involved in the ICI group were anti-PD1 (58 reports [63.7%]), anti-PD1 plus anti-CTLA4 (15 [16.5%]), anti-CTLA4 (13 [14.3%]), anti-PD-L1 (4 [4.4%]), and anti-PD1 plus anti-lymphocyte activation gene 3 (1 [1.1%]). An ICI was used in combination with a non-ICI anticancer agent in 10 participants (11.0%). Compared with other anticancer drugs, none of the 45 adverse outcomes identified were overreported in the group exposed to ICIs. However, preterm birth was significantly overreported for the anti-PD1 plus anti-CTLA4 combination compared with other anticancer drugs (12 of 15 [80.0%] vs 793 of 3452 [23.0%]; ROR, 13.87; 95% CI, 3.90-49.28; $P < .001$) but not for anti-PD-L1 or anti-CTLA4 monotherapy. Three reports of possibly immune-related maternofetal events were identified: 1 case of maternal antiphospholipid syndrome leading to spontaneous abortion, 1 case of pneumonitis leading to neonatal respiratory distress syndrome and death, and 1 case of transient congenital hypothyroidism.

(continued)

Key Points

Question Is exposure to immune checkpoint inhibitors (ICIs) during pregnancy associated with increased risk of adverse pregnancy, fetal, and/or newborn outcomes compared with exposure to other anticancer treatments?

Findings In this cohort study of 3558 reports with mentions of anticancer agent exposure during pregnancy from the World Health Organization's global pharmacovigilance database, exposure to ICIs (91 reports) was not associated with overreporting of specific adverse pregnancy, fetal, or newborn outcomes compared with exposure to other anticancer treatments (3467 reports).

Meaning The findings suggest that ICI use during pregnancy may be better tolerated than previously suspected.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this cohort study of 91 individuals exposed to ICIs during pregnancy, ICI exposure was not associated with overreporting of specific adverse pregnancy, fetal, and/or newborn outcomes compared with other anticancer treatments. However, due to possible rare immune-related neonatal adverse events, ICI use in pregnant women should be avoided when possible, especially the anti-PD1 plus anti-CTLA4 combination.

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Introduction

Pregnancy during active cancer treatment is a rare condition occurring in 0.1% of pregnancies and for 0.07% to 0.1% of all malignant tumors.¹ The main cancers associated with pregnancy are breast cancer, cervical cancer, Hodgkin disease, malignant melanoma, and leukemias.² The therapeutic management of pregnant individuals with cancer is particularly challenging since it involves both the mother and the fetus, and clinically reliable data are needed.

Immune checkpoint inhibitors (ICIs) are now widely prescribed for various malignant tumors.³ Immune checkpoint inhibitors, such as monoclonal antibodies blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA4), lymphocyte activation gene 3 (LAG3), and programmed cell death 1 (PD1) or its ligand (PD-L1), restore T cell-mediated immune response against multiple cancer types.⁴ However, ICIs may also impair immune tolerance, potentially increasing the risk of immune-related adverse events, including autoimmunity.⁵

The intricate process of maternofetal immunotolerance during pregnancy involves a complex interplay of immunomodulatory mechanisms in which the maternal immune system adapts to accommodate the presence of the semiallogenic fetus, thus preventing immune rejection and fostering a state of immune equilibrium critical for successful gestation.⁶ It is noteworthy that the expression of immune checkpoints (especially PD1) on T cells at the maternofetal interface increases as pregnancy progresses and is expected to prevent immune rejection of the fetus in utero.⁷⁻⁹ Anticancer immunotherapies may theoretically modify this maternofetal immune balance and might cause complications during pregnancy. The injection of a high dose of the anti-PD1 agent nivolumab (>10 times the clinical dose) in cynomolgus monkeys resulted in an increased risk of fetal growth restriction, premature delivery, and embryonal, fetal, and neonatal death compared with placebo, possibly due to increased interferon γ production.¹⁰

Despite pregnancy during cancer treatment being a rare condition, the intentional or unintentional use of ICIs for cancer in pregnant individuals is expected to rise. With the recent approval of anti-PD1 drugs for breast cancers, an increase in the exposure of pregnant individuals to ICIs is anticipated.¹¹ Currently, the use of ICIs during pregnancy is discouraged due to the absence of safety data obtained in the pregnancy setting.^{12,13} Given the major benefits associated with ICIs, data from large-scale studies exploring the toxic effects of these agents during pregnancy are crucial.

VigiBase is the World Health Organization's pharmacovigilance database and holds over 30 million specific case safety reports¹⁴ from over 130 countries dating back to 1967. This database is a valuable resource in uncovering new adverse drug reactions.^{15,16} In oncology,¹⁷ existing guidelines stipulate that medical professionals should closely observe and report any instances of pregnancy during both clinical trials and regular treatment. Recently, a study analyzed VigiBase reports involving ICI exposure during the peripregnancy period and potential associations with pregnancy-related outcomes.¹⁸ The analysis was restricted to spontaneous abortion, fetal growth restriction, and premature birth. Moreover, no multivariable or sensitivity analysis was performed, and no individual case or subgroup analysis was conducted.

In previous research using VigiBase, some of us performed a case-control disproportionality analysis to determine the reporting odds ratio (ROR) of pregnancy and/or fetal or newborn outcomes associated with exposure to anti-*ERBB2* drugs compared with exposure to other anticancer drugs.¹⁹

We found that individuals exposed to anti-*ERBB2* drugs during pregnancy were at higher risk of oligohydramnios (ROR, 17.68; 95% CI, 12.26-25.52; $P < .001$), fetal or neonatal kidney failure (ROR, 9.15; 95% CI, 4.62-18.12; $P < .001$), and congenital respiratory malformations (ROR, 9.98; 95% CI, 2.88-34.67; $P = .001$), in line with previously published evidence,^{20,21} thus validating the use of VigiBase as a useful resource to investigate the association of pregnancy, fetal, and/or newborn outcomes with anticancer drugs. This study gave evidence for the risk of oligohydramnios provoked by fetal kidney insufficiency that could, in some rare cases, lead to respiratory tract malformations.¹⁹

The objective of this cohort study was to perform a large-scale descriptive analysis of pregnancy, fetal, and/or newborn outcomes after exposure to ICIs and to determine the ROR of any adverse pregnancy, fetal, and/or newborn outcomes after exposure to ICI drugs compared with other non-ICI anticancer drugs in a case-noncase disproportionality analysis using a validated method.

Methods

Study Design and Data Protection

In this cohort study, we performed a case-noncase disproportionality analysis using pharmacovigilance individual case safety reports (hereafter, *reports*) from VigiBase to evaluate the association between the rate of maternal and fetal or newborn adverse outcomes and exposure to ICIs (ICI-exposed group) compared with exposure to other anticancer agents (ICI-unexposed group) in a cohort of reports of patients with cancer and anticancer drug exposure during pregnancy. The data in the VigiBase database are anonymized, and it is not possible to access personal information about the patients or the individuals reporting the cases; thus, informed consent was not required. We adhered to all applicable legislation, such as but not limited to European Union and national legislation regarding the protection of personal data (eg, the Data Protection Directive 95/46/EC and Regulation [EC] No. 45/2001, as applicable). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-noncase studies.²² The institutional review board of Institut Curie (Comité de Revue Institutionnelle-CRI Data) granted study approval.

Data Query and Report Extraction

VigiBase was queried on June 26, 2022, with the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. We extracted reports from VigiBase containing 1 or more pregnancy-related reactions and suspecting 1 or more anticancer drugs.

Reactions related to pregnancy were defined as any reaction with a reported term falling in the following MedDRA dictionary categories: *pregnancy, puerperium, and perinatal conditions* (system organ classification [SOC]) OR *fetal and neonatal investigations* (high-level group term [HLGT]) OR *neonatal and perinatal conditions* (HLGT) OR *neonatal respiratory disorders* (HLGT) OR *exposures associated with pregnancy, delivery, and lactation* (high-level term [HLT]) OR *fetal therapeutic procedures* (HLT) OR *induced abortions* (HLT) OR *obstetric therapeutic procedures* (HLT). Details are summarized in eTable 1 in [Supplement 1](#).

A report was considered to be suspecting an anticancer drug when 1 or more anticancer drugs were denoted as "suspect" (or "interacting"). Anticancer drugs were any drugs from the antineoplastic Anatomical Therapeutic Chemical (ATC) classification group L01.

Data Cleaning and Exclusion Criteria

We ensured that only reports mentioning pregnancy-associated conditions or exposure were retained by discarding reports with terms secondarily associated with pregnancy. Only reports with terms primarily associated with pregnancy as a main SOC, HLGT, or HLT were retained. Reports were then analyzed to discard those with no mention of a cancer diagnosis or with an antineoplastic drug from the L01 ATC group prescribed for a noncancer indication (eg, prescription of methotrexate for

rheumatoid arthritis or alemtuzumab for multiple sclerosis) and those with drug-mapping problems or adverse event-mapping problems (eTable 2 in [Supplement 1](#)).

Modality of Exposure During Pregnancy

Timing and modality of anticancer drug exposure were identified using preferred terms notified in reports for the timing and modality of exposure (eTable 3 in [Supplement 1](#)). Exposure types were exposure before pregnancy, exposure during pregnancy, exposure via breast milk, exposure via semen, and exposure via skin. Reports with a biological sex notified as male were considered to be exposed via semen. Reports with notification of a term associated with exposure via skin or semen were excluded. Reports with exposure via breast milk or before pregnancy and no specific mention of exposure during pregnancy were also discarded. All other reports were considered to include exposure to anticancer drugs during pregnancy.

Definition of Exposure Groups

We considered the following US Food and Drug Administration (FDA)-approved drugs to be ICI drugs: PD1 inhibitors (nivolumab, pembrolizumab, cemiplimab, and dostarlimab), PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab), or other FDA-approved checkpoint inhibitors (anti-CTLA4: ipilimumab and tremelimumab; anti-LAG3: relatlimab). Any report from the study analysis with a mention of an ICI drug was categorized in the ICI-exposed group. Each report in the ICI-exposed group was individually analyzed. Reports with exposure to other anticancer drugs and no mention of ICIs were categorized in the ICI-unexposed group.

Definition of Cases and Noncases for Maternal and Fetal or Newborn Outcomes

In the case-noncase disproportionality analysis, each maternofetal adverse outcome was analyzed independently. Cases were defined as study population reports with a mention of the adverse outcome. Noncases were defined as all other study reports with exposure to any anticancer drug and no mention of the adverse outcome. Adverse events of interest were maternal and fetal or newborn adverse outcomes mapped directly to MedDRA preferred terms in [VigiBase](#). They constituted 45 individual maternofetal adverse outcomes regrouped into 7 categories for the purposes of this study: abortion, stillbirth or fetal death, congenital malformation, pregnancy complication, preterm birth, neonatal complication, and delivery complication. Details of the fetal toxic effect subtypes explored are available in eTable 4 in [Supplement 1](#). Some adverse outcomes were deemed not clinically relevant and were discarded (eTable 5 in [Supplement 1](#)).

Statistical Analysis

We performed a case-noncase study using a disproportionality analysis to evaluate the association between an adverse outcome of interest and an exposure. The ROR was defined as the ratio of the odds of the adverse pregnancy, fetal, and/or newborn outcome of interest with exposure to ICIs (ICI-exposed group) to the odds of each outcome with exposure to other anticancer drugs (ICI-unexposed group).²³

The study population is described in terms of frequencies for qualitative variables and medians and IQRs for quantitative variables. Associations between categorical variables were assessed with χ^2 tests or Fisher exact tests if at least 1 category included fewer than 5 patients. Two-sided $P < .05$ was considered statistically significant. Analyses were conducted using R, version 4.1.3 (R Project for Statistical Computing).

To assess the robustness of our results, we conducted sensitivity and subgroup analyses on reports for which a single class of treatment was used (ICIs in the ICI-exposed group). For this analysis, any report with a combination of drug classes, such as cytotoxic drugs plus ICIs, was discarded. We also conducted a disproportionality analysis for each ICI regimen group: anti-PD1 or anti-PD-L1 alone, anti-CTLA4 alone, or both.

To limit the impact of biases, we also identified confounding variables using a directed acyclic graph (eFigure 1 in Supplement 1). We identified the year of report, the country of report, patient age, and the cancer type as main variables that need to be adjusted to limit confounding factors. The OR for the risk of each toxic effect was then evaluated using a multivariable analysis by logistic regression with adjustment for these variables. Missing data were grouped within a single level of value for each variable. To account for the type I error multiple comparison inflation test with the drug type analysis, we used Bonferroni correction to adjust *P* values.

Results

Report Characteristics

We extracted 9346 deduplicated reports and retained 3558 reports for the final analysis (ICI exposure: 91 [2.6%]; other anticancer drugs: 3467 [97.4%]) (Figure 1). Overall, the mean (SD) participant age was 28.7 (12.4) years. In all, 1713 reports (48.1%) were from the US, and breast cancer (685 reports [30.1%]) and chronic myeloid leukemia (611 reports [26.9%]) were the most frequently diagnosed cancers. Among reports for the group exposed to ICIs, most were from the US (60 [65.9%]), and the mean (SD) participant age was 28.9 (10.2) years. Melanoma (24 of 55 reports [43.6%]) and lymphoma (15 of 55 reports [27.3%]) were the 2 most frequently diagnosed cancers in the ICI group, whereas breast cancer (684 of 2220 reports [30.8%]) and chronic myeloid leukemia (611 of 2220 reports [27.5%]) were the 2 most frequent types of cancer in the other anticancer drugs group (Table 1 and eFigure 2 in Supplement 1).

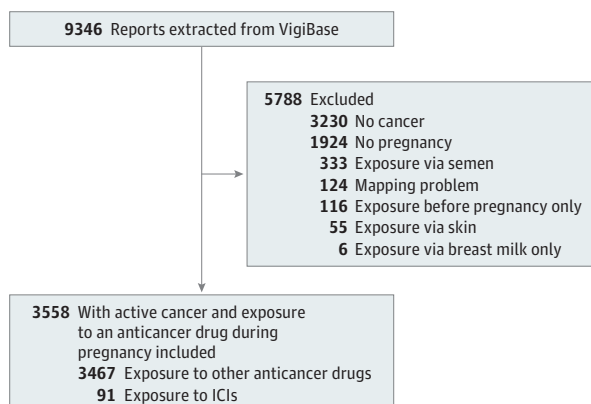
Exposure to Anticancer Drugs

The molecules involved in the ICI-exposed group were anti-PD1 (58 reports [63.7%]), anti-PD1 plus anti-CTLA4 (15 [16.5%]), anti-CTLA4 (13 [14.3%]), anti-PD-L1 (4 [4.4%]), and anti-PD1 plus anti-LAG3 (1 [1.1%]). Most reports in the ICI-exposed group involved only ICI drugs as anticancer agents (81 [89.0%]) (eFigure 3 in Supplement 1). An ICI was used in combination with a non-ICI anticancer agent in 10 participants (11.0%). In the other anticancer drugs group, 2029 reports (58.5%) mentioned a cytotoxic drug; 1884 (54.3%), a targeted therapy; and 94 (2.7%), other drug classes (Table 1).

Adverse Pregnancy, Fetal, and/or Newborn Outcomes

Adverse pregnancy, fetal, and/or newborn outcomes were reported in 38 reports in the ICI group (41.8%) and in 1980 reports (57.1%) in the other anticancer drugs group (ROR, 0.54; 95% CI, 0.35-0.82) (Figure 2 and eTable 6 in Supplement 1). There was no significant overreporting for any of the 45 pregnancy, fetal, and/or newborn adverse outcome types individually or grouped (Figure 2 and

Figure 1. Study Flowchart



All reports were extracted from VigiBase. Details of data extraction are provided in eTable 1 in Supplement 1. Terms associated secondarily with the VigiBase Medical Dictionary for Regulatory Activities (MedDRA) query terms were not specific to pregnancy and were discarded. Reports also mentioned a suspect or interacting drug from the anatomical and therapeutic chemical classification (ATC) LO1 (antineoplastic drugs) that could have been prescribed for a cancer or a noncancer indication. ICI indicates immune checkpoint inhibitor.

Table 1. Report Characteristics for the Cohorts With Exposure to ICIs or Other Anticancer Drugs

Variable	Reports ^a			P value
	Overall (N = 3558)	ICIs (n = 91)	Other anticancer drugs (n = 3467)	
Age, mean (SD), y ^b	28.7 (12.4)	28.9 (10.2)	28.7 (12.4)	.92
Country group				
Africa	113 (3.2)	0	113 (3.3)	
Americas, other ^c	130 (3.7)	5 (5.5)	125 (3.6)	
Asia	573 (16.1)	0	573 (16.5)	
Europe, other ^d	763 (21.4)	15 (16.5)	748 (21.6)	<.001
Germany	194 (5.5)	8 (8.8)	186 (5.4)	
Oceania	72 (2.0)	3 (3.3)	69 (2.0)	
US	1713 (48.1)	60 (65.9)	1653 (47.7)	
Notifier type, No./total No.				
Consumer or nonhealth professional	343/3314 (10.4)	14/88 (15.9)	329/3226 (10.2)	
Physician or pharmacist	1743/3314 (52.6)	50/88 (56.8)	1693/3226 (52.5)	.07
Other health professional	1228/3314 (37.1)	24/88 (27.3)	1204/3226 (37.3)	
Notifiers, No./total No.				
1	3016/3314 (91.0)	84/88 (95.5)	2932/3226 (90.9)	
≥2	298/3314 (9.0)	4/88 (4.5)	294/3226 (9.1)	.20
Year of first report				
≤2009	362 (10.2)	0	362 (10.4)	
2010-2014	918 (25.8)	2 (2.2)	916 (26.4)	
2015-2019	1611 (45.3)	56 (61.5)	1555 (44.9)	<.001
2020-2022	667 (18.7)	33 (36.3)	634 (18.3)	
Suspect or interacting drugs, No.				
1	1516 (42.6)	62 (68.1)	1454 (41.9)	
2	614 (17.3)	12 (13.2)	602 (17.4)	<.001
≥3	1428 (40.1)	17 (18.7)	1411 (40.7)	
Setting				
Clinical trial	31 (0.9)	7 (7.7)	24 (0.7)	
Routine care	3527 (99.1)	84 (92.3)	3443 (99.3)	<.001
Cancer subtype, No./total No. (%)				
Brain and nervous system	28/2275 (1.2)	1/55 (1.8)	27/2220 (1.2)	
Breast	685/2275 (30.1)	1/55 (1.8)	684/2220 (30.8)	
Colorectal and intestine	38/2275 (1.7)	4/55 (7.3)	34/2220 (1.5)	
Lung	42/2275 (1.8)	3/55 (5.5)	39/2220 (1.8)	
Lymphoma	295/2275 (13.0)	15/55 (27.3)	280/2220 (12.6)	
Melanoma	41/2275 (1.8)	24/55 (43.6)	17/2220 (0.8)	
Mesothelioma	1/2275 (0.0)	1/55 (1.8)	0	<.001
Ovarian, peritoneal, gestational, and germline	54/2275 (2.4)	1/55 (1.8)	53/2220 (2.4)	
Kidney	6/2275 (0.3)	4/55 (7.3)	2/2220 (0.1)	
Sarcoma	54/2275 (2.4)	1/55 (1.8)	53/2220 (2.4)	
Acute leukemia	182/2275 (8.0)	0	182/2220 (8.2)	
Chronic myeloid leukemia	611/2275 (26.9)	0	611/2220 (27.5)	
Other cancers	238/2275 (10.5)	0	238/2220 (10.7)	
Suspect molecule class				
Cytotoxic	2035 (57.2)	6 (6.6)	2029 (58.5)	<.001
Molecular targeted therapy	1889 (53.1)	5 (5.5)	1884 (54.3)	<.001
Non-ICI immunotherapy	12 (0.3)	0	12 (0.3)	<.001
Hormone therapy	75 (2.1)	0	75 (2.2)	.29
Other or NOS anticancer	7 (0.2)	0	7 (0.2)	>.99
Comedication	1082 (30.4)	17 (18.7)	1065 (30.7)	.02

Abbreviations: ICI, immune checkpoint inhibitor; NOS, not otherwise specified.

^a Data are presented as number (percentage) of reports unless otherwise indicated.

^b Values were missing for 42 ICI reports and 1992 reports of other anticancer drugs.

^c Countries in North and South America other than the US.

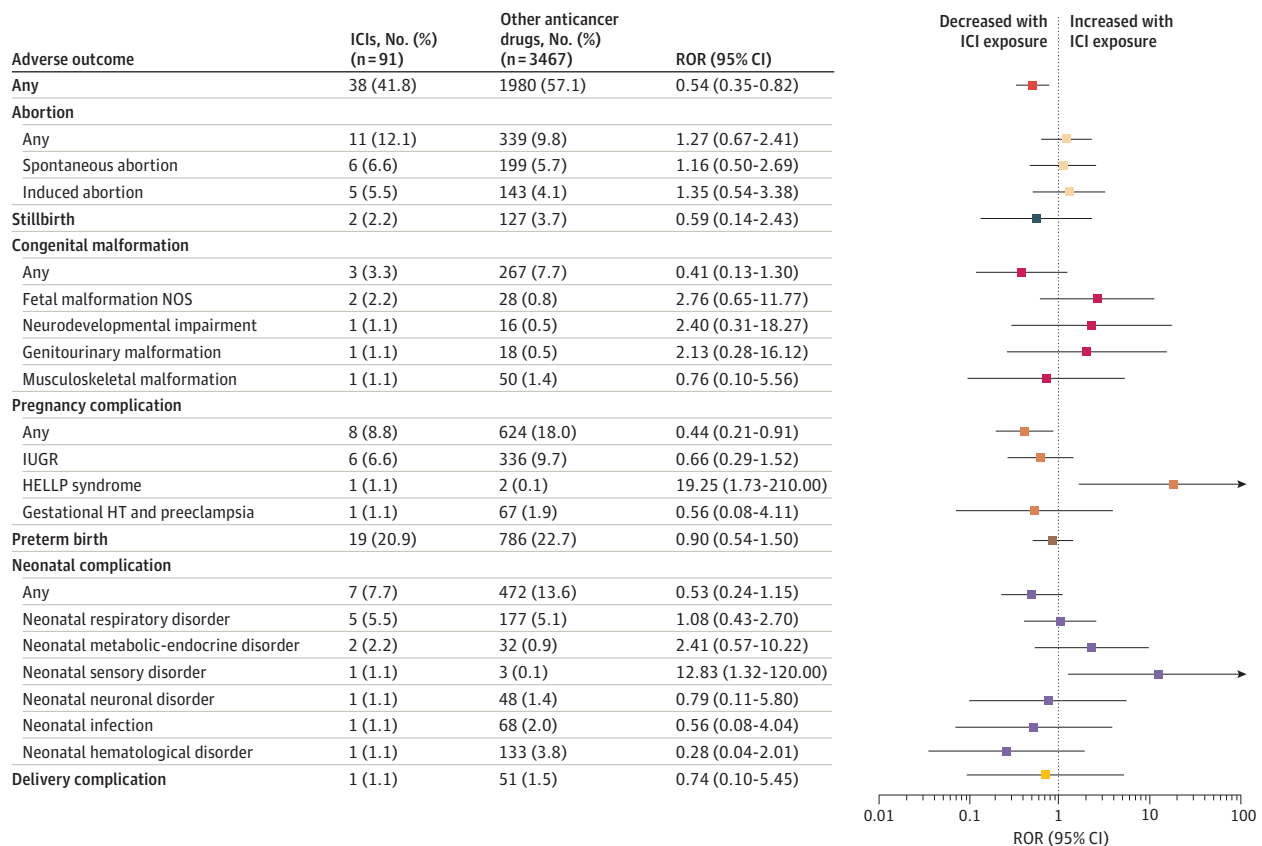
^d Countries in Europe other than Germany.

eTable 6 in Supplement 1). None of the terms deemed not clinically significant (eTable 5 in Supplement 1) were found within ICI-exposed reports. On analyzing the different types of ICI regimens, preterm birth was significantly overreported for the anti-PD1 plus anti-CTLA4 combination compared with other anticancer drugs (12 of 15 reports [80.0%] vs 793 of 3452 [23.0%]; ROR, 13.87; 95% CI, 3.90-49.28; $P < .001$) but not for anti-PD1 or anti-PD-L1 (6 of 63 reports [9.5%]; ROR, 0.36; 95% CI, 0.15-0.83) or anti-CTLA4 (1 of 13 reports [7.7%]; ROR, 0.28; 95% CI, 0.04-2.19) monotherapy (Figure 3 and eTable 7 in Supplement 1).

Sensitivity and Multivariable Analysis

In the multivariable analysis (eFigure 4 in Supplement 1), after adjustment for the year and country of the reports, individual's age, and tumor type, no maternofetal adverse outcome with 2 or more occurrences in the ICI-exposed group was overreported. The overall ROR remained significantly less than 1 in the ICI-exposed group (ROR, 0.61; 95% CI, 0.39-0.95). Induced abortion was the only overreported outcome (ROR, 3.37; 95% CI, 1.12-8.24). Similarly, sensitivity analysis performed on the subpopulation treated with ICIs only (81 reports [89.0%]) found similar results compared with other single-class anticancer drugs reports apart from those for preterm birth (ROR, 2.31; 95% CI, 1.35-3.94) (eFigure 5 in Supplement 1).

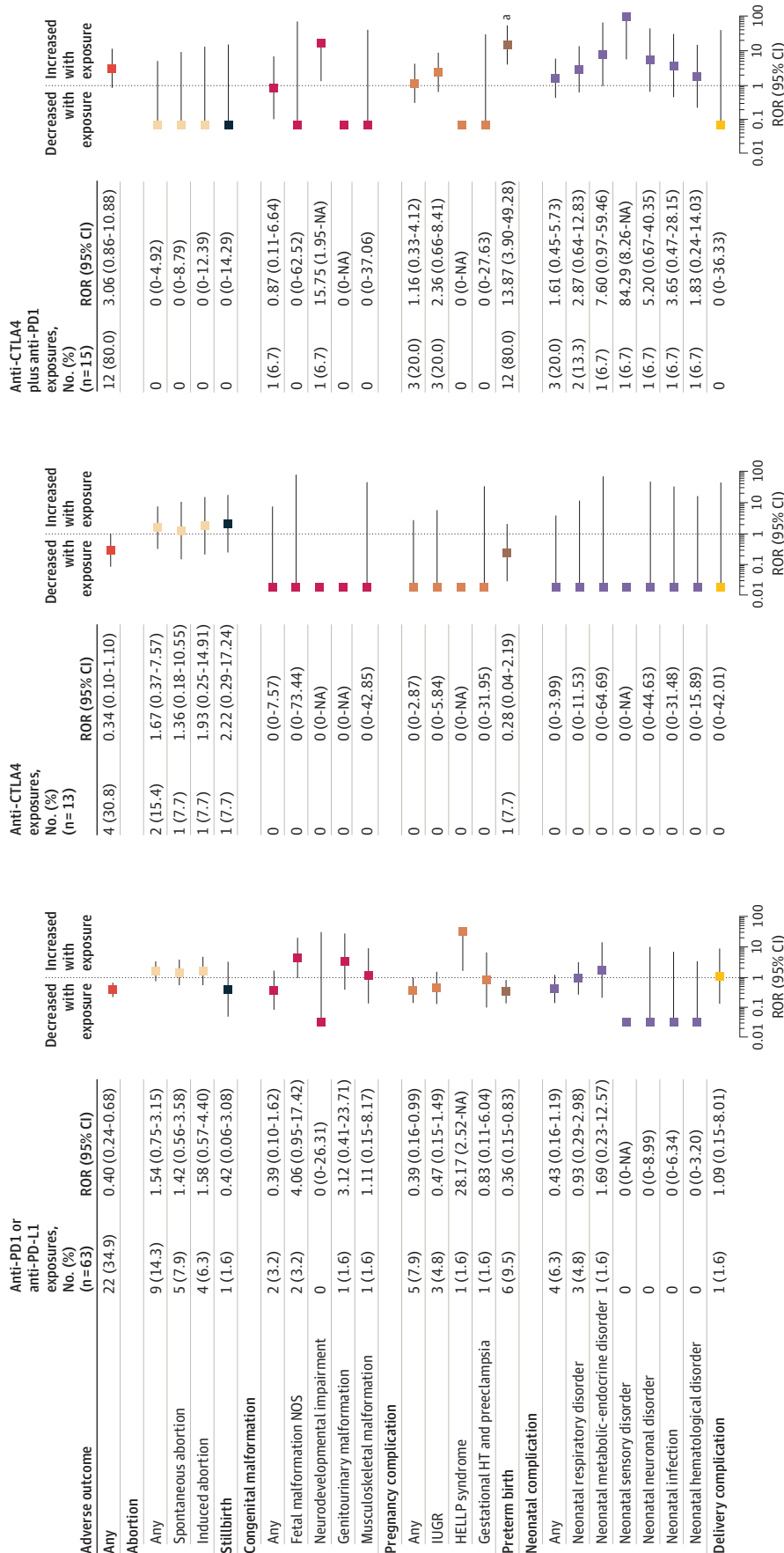
Figure 2. Description and Reporting Odds Ratios (RORs) of Adverse Pregnancy and Fetal or Newborn Outcomes After Exposure to Immune Checkpoint Inhibitors (ICIs) Compared With Exposure to Other Anticancer Drugs



Among the 45 prespecified maternofetal adverse outcome types, the figure shows toxic effects for which at least 1 case was found in the ICI-exposed group (eTable 4 in Supplement 1). Adverse outcomes with $n = 1$ were deemed not significant. HELLP

indicates hemolysis, elevated liver enzymes, and low platelets; HT, hypertension; IUGR, intrauterine growth restriction; and NOS, not otherwise specified.

Figure 3. Description and Reporting Odds Ratios (RORs) of Adverse Pregnancy and Fetal or Newborn Outcomes Associated With Exposure to Each Immune Checkpoint Inhibitor (ICI) Subtype



P values were adjusted for multiple comparisons using Bonferroni correction (4 analyses). Adverse outcomes with n = 1 were deemed not significant. CTLA4 indicates cytotoxic T-lymphocyte-associated protein 4; HELLP, hemolysis, elevated liver enzymes, and low platelets; HT, hypertension; IUGR, intrauterine growth restriction; NA, not applicable; NOS, not otherwise specified; PD1, programmed cell death 1; and PD-L1, programmed cell death 1 ligand.

^a P ≤ .001.

Reports of Interest

We identified 3 ICI reports with suspected immune-related pregnancy, fetal, and/or newborn complications (3.3%) (Table 2). One mother developed a combination of antiphospholipid syndrome, pneumonitis, and thyroiditis associated with spontaneous abortion (case 1). One report mentioned fetal pneumonitis, possibly immune-related and leading to neonatal respiratory distress syndrome (case 2). One newborn experienced intrauterine growth restriction, preterm birth, and transient congenital hypothyroidism (case 3).

In other reports, maternal immune-related thyroiditis and autoimmune hepatitis were associated with hemolysis, elevated liver enzymes, and low platelets syndrome and with a preterm birth (case 4). Three other reports indicated particularly severe outcomes, including 1 case of intrauterine growth restriction with congenital hand malformation, preterm birth, and neonatal respiratory disorder (case 5); 1 case of extreme prematurity with multiple severe complications (case 6); and 1 case of maternal hypophagia leading to stillbirth (case 7).

Discussion

In the present cohort study, we analyzed a large series of reports of maternofetal exposure to ICIs during pregnancy. We found no overreported outcomes in the group exposed to ICIs compared with the group exposed to other anticancer agents for all maternal, fetal, and newborn adverse outcomes explored.

First, we found that among the 91 reports in the ICI-exposed group, only 38 (41.8%) indicated pregnancy, fetal, and/or newborn complications. None of the 45 explored maternofetal outcomes were overreported in the ICI-exposed group compared with the group exposed to other anticancer drugs. These findings align with a recent pharmacovigilance study using VigiBase that revealed no discernible patterns of maternal, fetal, or newborn toxic effects and no signals of disproportionate reporting within the ICI group compared with the other anticancer agents group.¹⁸ However, that study had several limitations. First, it was not specifically focused on patients with cancer. Second, no multivariable or sensitivity analysis was conducted. Third, the authors restricted their analysis to spontaneous abortion, fetal growth restriction, and premature birth. Finally, the authors did not conduct individual case analysis or subgroup analysis based on the specific type of ICI used. Most of

Table 2. Reports of Particular Interest for Cases of Exposure to ICIs During Pregnancy^a

Case	Country	Year of first report	Mother's age, y	Cancer	Anticancer treatment	Maternal ADR	Pregnancy event	Fetal-newborn outcome
1	US	2021	30s	Stage III melanoma	Adjuvant pembrolizumab	Antiphospholipid syndrome, pneumonitis, thyroiditis ^b	Spontaneous abortion	Spontaneous abortion
2	UK	2021	NR	Non-small cell lung cancer	Pembrolizumab, carboplatin, pemetrexed	None	None	Neonatal respiratory syndrome, pneumonitis, neonatal death ^c
3	Australia	2019	30s	Melanoma	Nivolumab, ipilimumab	None	IUGR	Transient congenital hypothyroidism, preterm birth
4	Germany	2019	30s	Uveal melanoma	Nivolumab	Autoimmune hepatitis, thyroiditis ^d	HELLP syndrome, twin pregnancy	Preterm birth
5	Germany	2019	NR	NR	Nivolumab	None	IUGR	Congenital hand malformation; fetal distress and neonatal respiratory disorder; preterm birth
6	Germany	2017	30s	Melanoma	Nivolumab, ipilimumab	None	None	Extreme prematurity complications: retinopathy, stroke, neonatal respiratory distress, motor developmental delay
7	US	2018	20s	Hodgkin lymphoma	Nivolumab	Nondiabetic ketoacidosis with starvation or hypophagia	Stillbirth	Stillbirth

Abbreviations: ADR, adverse drug reaction; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; ICI, immune checkpoint inhibitor; IUGR, intrauterine growth restriction; NR, not reported.

^a Reports with maternofetal events of particular interest were summarized.

^b The maternal ADR was considered immune related for all conditions.

^c The maternal ADR was considered immune related for pneumonitis.

^d The maternal ADR was considered immune related for thyroiditis.

the remaining literature focuses on particularly unfavorable maternofetal outcomes, leading authors to highlight the importance of risk of maternofetal toxic effects.^{10,24,25} Of 7 cases of maternofetal exposure to ICIs previously described in the literature, only 2 did not have any pregnancy or newborn complication reported.²⁴ Mittra and colleagues²⁶ reported 8 cases of ICI-exposed pregnancies among 635 trials. For 2 cases, induced abortion was reported, and for 1 case, preeclampsia and prematurity were reported. Five other cases had no pregnancy complication and led to healthy newborns, and this case series balanced previous conclusions. However, the small sample size and the fact that only cases from clinical trials were reported make the conclusion difficult to extrapolate. In the present study, we found overreporting of maternofetal exposure to ICIs not associated with pregnancy, fetal, or newborn complications compared with exposure to other anticancer drugs (eTable 6 in Supplement 1), which suggests that maternofetal exposure to ICIs might be safer in routine care than reported in a previous study.^{10,24,25} In the multivariable analysis, induced abortion was the only outcome overreported in the ICI-exposed group (eFigure 4 in Supplement 1). The absence of comparative safety data on ICIs and the initial high risk expected to be associated with fetal exposure to ICIs¹⁰ could explain this result.

Second, to our knowledge, no study to date has examined the risk of maternofetal adverse drug reactions associated with ICIs based on the specific type of ICI. In the current study, preterm birth was significantly overreported with the anti-PD1 and anti-CTLA4 combination and not with anti-PD1, anti-PD-L1, or anti-CTLA4 monotherapy. The combination of anti-PD1 and anti-CTLA4 is widely recognized for its higher toxicity compared with ICI monotherapy.^{27,28} This observation seems to support findings in the current study of ICI exposure during pregnancy, as there was overreporting of prematurity in the ICI combination therapy group compared with ICI monotherapy group. The maternal immune system undergoes modulation during pregnancy, establishing tolerance to the semiallogenic fetus expressing both maternal and paternal antigens.²⁹ At the maternofetal interface, known as the uterine decidua, a pivotal role is played in immunologic protection and the production of essential hormones, enzymes, and cytokines for a successful pregnancy.³⁰ Interactions among components comprising trophoblasts, decidual stromal cells, and immune cells are critical for the regulation of trophoblast invasion, placental development, and fetomaternal tolerance (eTable 8 in Supplement 1). Immune checkpoints, such as the PD1-PD-L1 pathway, are crucial in these interactions. Dysfunction in this pathway leading to inadequate T-cell inhibition can result in adverse pregnancy outcomes.³¹ Another vital inhibitory immune signaling pathway involves CTLA4 and its ligands CD80 and CD86. CTLA4, primarily expressed by regulatory T cells in the decidua, contributes to inducing peripheral tolerance and Treg-mediated suppression in mice.³² Considering the potential compensation between signaling pathways, the dysfunction of one (PD1-PD-L1, CTLA4-CD80, or CTLA4-CD86) could be offset by the other. This could elucidate the higher incidence of preterm birth in patients undergoing combined treatment with anti-PD1 and anti-CTLA4, as the pathological pathways leading to late preterm birth predominantly involve anti-fetal rejection. Therefore, use of a combination of anti-PD1 or anti-PD-L1 with anti-CTLA4 in pregnant individuals should be avoided when possible.

Third, for a few cases, we found maternofetal complications that could have been linked to autoimmunity and immune-related complications. In 1 case (case 1; Table 2), antiphospholipid syndrome (APS) led to spontaneous abortion. Antiphospholipid syndrome is an autoimmune systemic disorder characterized by arterial or venous thrombosis, which can lead to spontaneous abortion, fetal loss, or pregnancy morbidities.³³ No report of APS was present in the noncase cohort, and APS could have been caused by immune activation of ICIs.⁵ We observed 1 case of transient congenital hypothyroidism (case 3; Table 2); this could have been due to maternal antibodies, although no concomitant maternal immune-related adverse event or adverse drug reactions were reported. Transient congenital hypothyroidism has been reported to be associated with maternal autoimmunity in the population without cancer,³⁴ and ICI-induced autoimmunity could have caused this neonatal complication. We also observed a case of neonatal respiratory distress syndrome with concomitant acute interstitial pneumonitis, possibly due to maternal autoimmunity. However, the

report was too scarce to draw definitive conclusions about the association between maternal and neonatal outcomes. These observations underscore the potential for rare but potentially severe immune-mediated maternofetal adverse events, as exemplified by a recently documented case of gastroenterocolitis.²⁵ In this instance, persistent diarrhea and failure to thrive following in utero exposure to anti-PD1 were subsequently diagnosed as immune-related enterocolitis and effectively managed with prednisolone and infliximab.²⁵

Limitations

This study has limitations due to inconsistencies in the data collection methods used in pharmacovigilance. The lack of specific details about the timing of exposure complicates analysis of how the length of fetal exposure impacts outcomes. Other limitations encompassed the absence of precise data on tumor stage, treatment setting, and treatment outcomes. However, sensitivity analysis carried out among more homogeneous subgroups and multivariable analyses adjusted for key variables consistently reaffirmed our primary findings. Nonetheless, this approach could not quantitatively apprehend the onset of rare and diverse immune-mediated events, as observed in our cases of interest. Furthermore, caution is advised in interpreting the increased rate of preterm birth associated with the combination of anti-PD1 or anti-PD-L1 plus anti-CTLA4, as the treatment is typically used for metastatic tumors. Conversely, anti-PD1 or anti-PD-L1 monotherapy is also prescribed in the perioperative setting, where the risk-benefit profile of the treatment significantly varies. Another constraint lies in the absence of information regarding the gestational term of preterm birth in patients exposed to the anti-PD1 or anti-PD-L1 and anti-CTLA4 combination. This limitation hinders the comprehensive interpretation of these cases.

Conclusion

In this cohort study of 91 individuals exposed to ICIs during pregnancy, ICI exposure was not associated with overreporting of specific adverse pregnancy, fetal, and/or newborn outcomes compared with other anticancer treatments. The findings suggest that use of ICIs during pregnancy seems to be better tolerated than previously suspected. However, due to possible rare immune-related neonatal adverse events, ICI use, especially the anti-PD1 or anti-PD-L1 plus anti-CTLA4 combination, in pregnant women should be avoided when possible. The risk-benefit evaluation for both the mother and the fetus or newborn should be discussed case by case considering the oncologic urgency. Systematic routine abortion may not be recommended, although thorough monitoring of newborns is warranted.

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SUPPLEMENT 1.

eTable 1. Detail of VigiBase Query

eTable 2. Terms Corrected

eTable 3. MedDRA Preferred Terms Used to Qualify Reports' Exposure Type

eTable 4. Individual Maternofetal Adverse Outcomes Explored

eTable 5. Terms Deemed Not Clinically Significant

eTable 6. Details of Pregnancy and/or Fetal or Newborn Outcomes in the ICI-Exposed Group Compared With the Group Exposed to Other Anticancer Drugs

eTable 7. Details of Pregnancy and/or Fetal or Newborn Outcomes in the ICI-Exposed Subpopulation Compared With the Population Exposed to Other Anticancer Drugs

eTable 8. Relevant Immune Checkpoints and Their Ligands on Decidual Immune Cells

eFigure 1. Directed Acyclic Graph for Assessment of Confounding Factors

eFigure 2. Characteristics of Reports in the Study Population

eFigure 3. UpSet Plot of the Reporting of Anticancer Drugs in the ICI-Exposed Group

eFigure 4. Multivariable Analysis of the Risk of Adverse Outcomes

eFigure 5. Sensitivity Analysis Within the Subpopulation Treated With Single-Class Drugs

SUPPLEMENT 2.

Data Sharing Statement