Immune Checkpoint Inhibitor Exposure in Pregnancy: A Scoping Review

Iman Salehi,* Ludmila Porto,† Christine Elser,‡ Jessica Singh,§ Samuel Saibil∥ and Cynthia Maxwell†

Summary: Since their approval, immune checkpoint inhibitors (ICIs) have become the standard of care for multiple malignancies. ICIs enhance tumor destruction by blocking important immunomodulatory pathways that regulate T-cell activation. These pathways include programmed cell death protein-1 and its ligands (programmed cell death protein-1 and programmed death ligand-1, respectively) and cytotoxic T-lymphocyte-associated protein 4. While blocking these pathways can enhance tumor destruction, these pathways are critical for the development of maternal tolerance towards the fetus. Therefore, if ICIs disrupt these immunomodulatory pathways, there could be a maternal immune response against the fetus, as was found in animal studies. With few reported cases of human pregnancy exposure to ICIs, the effects of ICIs on human pregnancy remain largely unknown. Here, we review and summarize the 6 cases of maternal exposure to immunotherapy that have been published before the present study. To add to the evidence, we present a case series of 2 patients who have been exposed to immunotherapy in pregnancy.

Key Words: pregnancy, cancer, immunotherapy, radiation

Since the approval of ipilimumab in 2011, immune checkpoint inhibitors (ICIs) have become the backbone of treatment for a growing number of malignancies. There have been few case reports on ICI exposure during pregnancy.1,2 A cancer diagnosis in pregnancy is uncommon, complicating 0.02%–0.1% of all pregnancies.3,4 Breast cancer, hematological malignancies, cervical cancer, and melanoma are among the most diagnosed cancers in pregnancy.5,6 Despite the relatively low number of cases, the occurrence of several age-dependent malignancies in pregnancy is expected to rise, as decisions to delay childbearing is becoming increasingly common.7

Immunotherapy is becoming an increasingly common component of cancer therapy, and the incidence of cancer in pregnancy is on the rise. Therefore, it is of great importance to understand the effect of immunotherapy exposure on maternal and fetal outcomes. Commonly used ICIs, the immunomodulatory checkpoints they target, and the cancer-specific Food and Drug Administration (FDA) approval of each treatment are shown in Table 1.

BACKGROUND

Pregnancy entails physiological changes in all maternal systems, including alterations at different levels of the maternal immune system. Since the pregnant person and fetus are genetically discordant, the pregnant person must develop a tolerance to the fetus to allow the coexistence of 2 genetically distinct organisms.8–10 Programmed cell death protein-1 (PD-1) and its ligands (PD-L1 and PD-L2) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) have been linked to the development of maternal tolerance towards the fetus.11 The existence of these immune checkpoints is essential to induce a maternal immune tolerance to prevent the existence rejection of the semiallogenic fetus by regulating maternal T-lymphocyte activation.12 Moreover, the available drugs that inhibit these pathways are immunoglobulin (Ig) G4 antibodies, which can traverse the placenta and potentially cause direct teratogenic effects to the fetus.13 As expected from their ability to regulate undesirable immune responses, the PD-1, and CTLA-4 pathways are expressed at the maternal-fetal interface during pregnancy.14–20 Figures 1A, B, 2A, and B illustrate how these immune checkpoints interact with the immune system and how ICIs might interfere.

PD-1

PD-1 is a receptor expressed by T cells, B cells, natural killer cells, and antigen-presenting cells (APCs).21,22 PD-1 generates a strong inhibitory signal when bound to its ligands, PD-L1 and PD-L2, resulting in an inhibition of T-cell activity.23

Compared to the peripheral immune system, PD-1 expression is significantly elevated on the surface of decidual CD8+, CD4+, and regulatory T (Treg) cells.24 The increased expression of PD-1 on the surface of T cells at the maternal-fetal interface has emerged as a central function in maintaining immune tolerance in pregnancy.25

While the immunologic acceptance of the fetus is largely determined by maternal tolerance mechanisms at the maternal-fetal interface, it also has a significant effect on systemic immunity.26 The frequency of PD-1 expression on the surfaces of T cells and soluble PD-L1 levels in the blood of pregnant patients have been shown to be elevated compared with nonpregnant patients.27

The implications of blocking the PD-1 pathway have been shown through studies of murine models of allogeneic pregnancy.19 Treatment with anti-PD-L1 monoclonal antibodies (mAb) resulted in a 5-fold increase in the rate of spontaneous abortion of allogeneic (CBA×C56BL/6) murine concepti from 18% to 86%. In contrast, no significant

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From the *Mount Sinai Hospital; †Mount Sinai Hospital, University of Toronto; ‡Princess Margaret Cancer Centre, Mount Sinai Hospital, University of Toronto; §Simcoe Muskoka Regional Cancer Program, Royal Victoria Regional Health Centre; and ||Princess Margaret Cancer Centre, Toronto, ON, Canada.
Reprints: Cynthia Maxwell, OPG 3-901, Sinai Health, 700 University Avenue, Toronto, ON, Canada M5G1Z5 (e-mail: cynthiadr.maxwell@sinahealth.ca).
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### TABLE 1. Common Drugs That Inhibit the Activity of Important Immune Checkpoints

| Immune Checkpoint | Immune Checkpoint Inhibitor | FDA Approval | 
|-------------------|-----------------------------|--------------|
| PD-1              | Nivolumab (Opdivo)          | Melanoma, NSCLC, RCC, cHL, HNSCC, urothelial carcinoma, CRC, HCC |
|                   | Pembrolizumab (Keytruda)    | Melanoma, NSCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, CRC, gastric cancer, cervical cancer, HCC, MCC |
|                   | Cemiplimab (Libtayo)        | CSCC         |
| PD-L1             | Atezolizumab (Tecentriq)    | Urothelial carcinoma, NSCLC, TNBC |
|                   | Durvalumab (Imfinzi)        | NSCLC, urothelial carcinoma |
|                   | Avelumab (Bavencio)         | MCC, urothelial carcinoma |
|                   | Ipilimumab (Yervoy)         | Melanoma     |
| CTLA-4            |                             |              |

cHL indicates classic Hodgkin lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

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**FIGURE 1.** A, An illustration of the PD-1/PD-L1 pathway at baseline, before immune checkpoint inhibitor exposure. If PD-1 is bound to PD-L1, there is no T-cell activation and an immunotolerant effect toward the fetus is observed. B, An illustration of the PD-1/PD-L1 pathway after exposure to immune checkpoint inhibitors. The introduction of an anti-PD-1/PD-L1 monoclonal antibody promotes T-cell activation (enhancing tumor destruction) and possible fetal rejection. PD-1 indicates programmed cell death-1; PD-L1, programmed cell death ligand-1.
effects were noted upon antimurine PD-L1 mAb exposure in syngeneic (CBA × CBA) concepti. In the same experiment, fetal rejection of allogeneic mice concepti was confirmed to be T cell but not B-cell dependent in 2 ways. First, by using immunohistochemistry of placental sections, it was determined that T-cell infiltration clustered at the fetal resorption site in anti-PD-L1 treated animals with allogeneic pregnancy. Second, treatment with antimurine PD-L1 mAb significantly increased fetal rejection in B-cell–deficient females, but not in female mice who lacked both T cells and B cells.

The effect of blocking PD-L1 was further shown to be dependent on the presence of Treg cells. The enzyme indoleamine 2,3-dioxygenase present on trophoblastic giant cells in mice and on villous and extravillous trophoblasts in humans degrades tryptophan. It has been hypothesized that the deprivation of tryptophan inhibits the proliferation of maternal T cells and drives the generation of Treg cells.

Habicht et al showed significantly increased fetal resorption in murine models related to the depletion of Treg cells; control mice treated with IgG experienced an 18.8% rate of spontaneous abortion, whereas mice treated with anti-CD25, which is constitutively expressed on Treg cells, experienced a 31.9% rate of a fetal resorption.

Furthermore, Wafula et al found that blocking PD-L1 was dependent on the presence of Treg cells. This experiment showed that PD-1 was a fundamental mediator of Treg-induced fetal protection in a model of abortion-prone murine models (CBA/J × DBA/2J). These abortion-prone mice, lacking Treg cells, were transfused with Treg cells from normal pregnant mice and subsequently experienced normal pregnancy. After restoring normal pregnancy...
TABLE 2. Reported Cases of Immune Checkpoint Exposure in Pregnancy

|                  | Mehta et al<sup>1</sup>          | Burotto et al<sup>2</sup>          | Xu et al<sup>3</sup>          |
|------------------|----------------------------------|-----------------------------------|--------------------------------|
| Maternal age (y) | 34                               | Unknown                           | 32                            |
| Singleton or twins | Unknown                        | Unknown                           | G0P0                           |
| Gene status      | BRAF V600E mutant               | BRAF V600E mutant                  | BRAF V600E mutant              |
| Cancer type      | Metastatic melanoma             | Metastatic melanoma                | Metastatic melanoma            |
| Site of metastasis | Cutaneous in-transit, subcutaneous, nodal | None                             | Nodal, lung, liver             |
| Systemic treatment before pregnancy | Vemurafenib                  | Ipilimumab (3 mg/kg)+nivolumab (1 mg/kg) q2w | Nivolumab (3 mg/kg) q2w         |
| Systemic treatment at point of conception | Ipilimumab (3 mg/kg q3w) +intrallesional IL-2 (aldesleukin) | None                           | Nivolumab (3 mg/kg) q2w         |
| Systemic treatment given during pregnancy | Ipilimumab (3 mg/kg q3w) and intrallesional IL-2 in the first trimester, continued after discovery of pregnancy but ceased before the second trimester | Ipilimumab (3 mg/kg)+nivolumab (1 mg/kg) initiated during the first trimester, ceased in the second trimester due to immune hepatitis | Nivolumab (3 mg/kg) q2w in the first trimester, ceased upon discovery of pregnancy in the first trimester |
| Maternal iRAE before pregnancy | G1 diarrhea                   | NA                                | G3 GGT elevation               |
| Maternal iRAE during pregnancy | Nil                           | Immune hepatitis with G3 bilirubin rise, G3 AST/ALT elevation; G4 GGT elevation | Nil                           |
| Immunosuppressive therapy given during pregnancy | Not required                 | Steroids+azathioprine for immune hepatitis | Not required                 |
| Maternal disease response during pregnancy | PD of in-transit and nodal disease | Mixed response with reduction in liver and bone metastases, but progression in breast, lung metastases, and new brain metastases | Sustained CR                   |
| Maternal disease response after pregnancy | Further PD despite switch to pembrolizumab | PD to immunotherapy, PR after switch to vemurafenib | Sustained CR at 7 mo postpartum |
| Delivery date and modality | Unknown                      | 32/40 elective delivery by LUSCS  | 33/40 spontaneous premature labor, delivery by LUSCS |
| Obstetric complications | Nil                          | Placental insufficiency, nonpainful contractions, placental calcifications, and low fetal heart rate | IUGR                         |
| Placental melanoma involvement | Unknown                     | Unknown                           | No                            |
| Fetal melanoma transmission | No                           | No                               | No                            |
| Fetal iRAE | Nil                             | Nil                              | Congenital hypothyroidism      |
| Fetal outcome | Normal development at 2.75 y   | Normal development at 11 mo      | Normal development at 6 mo     |

|                  | Menzer et al<sup>4</sup>          | Bucheit et al<sup>5</sup>          | Haiduk and Ziemer<sup>6</sup>          |
|------------------|----------------------------------|-----------------------------------|-------------------------------------|
| Maternal age (y) | 34                               | Unknown                           | 39                                |
| Singleton or twins | Unknown                        | Unknown                           | Unknown                            |
| Gene status      | NRAS Q61 mutant                 | BRAF V600E mutant                 | Twin                              |
| Cancer type      | Metastatic melanoma             | Metastatic melanoma               | No mutations detected              |
| Site of metastasis | Lung, pleura, nodal, spine, liver, spleen | Nodal, breast, peritoneal space, brain, ovarian | Pulmonary micronodules            |
| Systemic treatment before pregnancy | None                          | Ipilimumab (3 mg/kg q3w) +nivolumab (1 mg/kg q3w) | Nivolumab (240 mg) q2w          |
| Systemic treatment at point of conception | Ipilimumab (3 mg/kg q3w)+nivolumab (1 mg/kg q3w) initiated during the first trimester, ceased at week 24 +2 after the second cycle | Ipilimumab (3 mg/kg q3w)+nivolumab (1 mg/kg q3w) for 4 cycles, then changed to single-agent nivolumab, ceased 7d before the cesarean section | Nivolumab (240 mg) q2w, suspended at 6wk gestation upon discovery of pregnancy |
| Systemic treatment given during pregnancy | None                          | G3 rash; G3 thrombocytopenia (both from vemurafenib exposure) | Elevated liver enzymes          |
| Maternal iRAE before pregnancy | NA                            | G3 rash                           | Suspected immune hepatitis due to history of elevated liver enzymes |
| Maternal iRAE during pregnancy | Nil                           | Nivolumab                         | Azathioprine for suspected immune hepatitis (discontinued after discovery of pregnancy) |
| Immunosuppressive therapy given during pregnancy | Not required                 | Not required                      |                                    |

<sup>1</sup> Mehta et al, 2020
<sup>2</sup> Burotto et al, 2020
<sup>3</sup> Xu et al, 2020
<sup>4</sup> Menzer et al, 2020
<sup>5</sup> Bucheit et al, 2020
<sup>6</sup> Haiduk and Ziemer, 2020
| Mehta et al<sup>1</sup> | Burotto et al<sup>2</sup> | Xu et al<sup>4</sup> |
|-----------------------|------------------------|-----------------------|
| **Maternal disease response during pregnancy** | Mother died from underlying disease 1 d after delivery | No progression during pregnancy | No progression after cessation of nivolumab at 6 wk |
| **Maternal disease response after pregnancy** | NA | New nodular enhancement in brain; No other sites of metastatic disease | CR at 9 mo postpartum |
| **Delivery date and modality** | 24+2/40 introduction of lung maturation in the infant, delivery by emergent cesarean section | 32/40, course of betamethasone for fetal lung maturity before delivery, delivery by cesarean section | 30/40, delivery due to maternal development of HELLP syndrome |
| **Obstetric complications** | Nil | IUGR | Hemolysis, elevated liver enzymes, low platelet count (HELLP syndrome) |
| **Placental melanoma involvement** | Yes, but only at the maternal site | No | No |
| **Fetal melanoma transmission** | No | No | No |
| **Fetal iRAE** | Nil | Nil | Nil |
| **Fetal outcome** | Other than prematurity-related complications, normal development at 12 mo | Both infants were admitted into NICU where they did well; also did well at home. No long-term report of their development | Smaller twin missing left hand (likely due to amniotic cord strangulation), normal development at 9 mo |

**Case Presentation 1**
- **Maternal age (y):** 34
- **Maternal parity:** G2P2
- **Singleton or twins:** Singleton
- **Gene status:** No mutations detected
- **Cancer type:** Metastatic melanoma
- **Site of metastasis:** Brain, abdominal wall, chest subcutaneous, pelvis subcutaneous, nodal, pulmonary
- **Systemic treatment before pregnancy:** None
- **Systemic treatment at point of conception:** Ipilimumab (3 mg/kg)+nivolumab (1 mg/kg) for 1 cycle
- **Maternal iRAE before pregnancy:** NA
- **Maternal iRAE during pregnancy:** G3 immune hepatitis; elevated (but stable) liver enzymes including G3 AST elevation; G1 ALT elevation; normal bilirubin levels
- **Immunosuppressive therapy given during pregnancy:** Steroids for elevated liver enzymes
- **Maternal disease response during pregnancy:** Extensive (but stable) metastatic disease after the dose, including intra-axial progression
- **Maternal disease response after pregnancy:** Mild improvement in brain metastases; mixed response extracranially
- **Delivery date and modality:** 31/40, antenatal steroids were given for fetal lung maturation, delivery by elective cesarean section
- **Obstetric complications:** Nil
- **Placental melanoma/renal involvement:** No
- **Fetal melanoma transmission:** No
- **Fetal iRAE:** Nil
- **Fetal outcome:** Infant showed normal development with no signs of metastatic melanoma

**Case Presentation 2**
- **Maternal age (y):** 33
- **Maternal parity:** G0P0
- **Singleton or twins:** Singleton
- **Gene status:** No genetic testing performed
- **Cancer type:** Renal cell carcinoma
- **Site of metastasis:** Pulmonary, left adrenal gland, nodal, spine, retroperitoneum
- **Systemic treatment before pregnancy:** Gemcitabine+cisplatin for 3 cycles; nivolumab+ipilimumab
- **Systemic treatment at point of conception:** Nivolumab
- **Maternal iRAE before pregnancy:** Nil
- **Maternal iRAE during pregnancy:** G3 immune hepatitis; elevated (but stable) liver enzymes including G3 AST elevation; G1 ALT elevation; normal bilirubin levels
- **Immunosuppressive therapy given during pregnancy:** Steroids for elevated liver enzymes
- **Maternal disease response during pregnancy:** Increase in size of retroperitoneal nodule and multilobulated lesion along the left gonadal vessels; spinal metastases remained unchanged
- **Maternal disease response after pregnancy:** Postnatally, patient resumed immunotherapy with nivolumab
- **Delivery date and modality:** 38/40, delivery by emergency cesarean section
- **Obstetric complications:** Arrest of cervical dilation and abnormal fetal heart tracing
- **Placental melanoma/renal involvement:** No
- **Fetal melanoma transmission:** No
- **Fetal iRAE:** Nil
- **Fetal outcome:** Infant showed normal development with no signs of renal metastases

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; CVD, cisplatin, vinblastine, dacarbazine; GGT, γ-glutamyltransferase; IL-2, interleukin-2; iRAE, immune-related adverse event; IUGR, intrauterine growth restriction; LUSCS, lower uterine segment cesarean section; NA, not available; NICU, neonatal intensive care unit; PD, progressive disease; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks.
in CBA/J×DBA/2J mice, treatment with anti-PD-1 mAb abolished the protective effects of Tregs and showed increased abortion rates similar to the abortion-prone mating of CBA/J×DBA/2J mice. This experiment provides compelling evidence that PD-1 has a fundamental role in Treg-mediated fetal protection in murine models.

In the DART study, pregnant cynomolgus monkeys exposed to nivolumab, an anti-PD-1 mAb, experienced a non-dose-related increase in the rate of spontaneous abortion and premature infant death, especially in the third trimester of pregnancy (US FDA, Reference ID: 4421379). No teratogenic effects were observed in monkeys exposed to nivolumab. In the surviving infants exposed to nivolumab in utero, there were no visible malformations and no effects on neurobehavioral, immunologic, or clinical pathology outcomes throughout the 6-month postnatal period.

**CTLA-4**

CTLA-4 is an inhibitory receptor that is primarily and constitutively expressed on the cell surface of Treg cells. The inhibitory effects of CTLA-4 stem from its competition with CD28 for binding the B7 ligands (CD80/86) found on the cell surface of APCs. CD28 is also a receptor that is constitutively expressed on the cell surface of T cells, and it provides a costimulatory signal for T-cell activation when bound to the B7 ligands on APCs.

Studies have suggested that the primary function of CTLA-4 is not to act as an inhibitory signal when bound to the B7 ligands. Instead, these studies suggest that CTLA-4 removes the B7 ligands from the cell surface of APCs, thereby preventing the binding of the B7 ligands to the costimulatory CD28 found on the surface of Treg cells. Therefore, the inhibition of the CTLA-4 checkpoint by anti-CTLA-4 antibodies results in T-cell activation, which is expected to cause adverse effects on pregnancy.

In the DART study, pregnant cynomolgus monkeys exposed to ipilimumab, an anti-CTLA-4 mAb, experienced a dose-related increase in abortion, stillbirths, premature delivery, and higher incidences of infant mortality, beginning in the third trimester. No treatment-related adverse effects were identified with ipilimumab exposure during the first 2 trimesters of pregnancy. In addition, developmental abnormalities of the urogenital system were identified in 2 infant monkeys exposed to nivolumab. One female infant developed unilateral renal agenesis of the left kidney and ureter, and 1 male infant developed an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema (US FDA, Reference ID: 4248855).

**Cases of Human Exposure in Pregnancy**

There have been no reported cases of humans exposed to ICIs in pregnancy until recently. Upon conducting an extensive literature search, we identified 6 patients exposed to ICIs during pregnancy from 2018 to 2021. These patients were treated for metastatic melanoma with either single-agent or combined immunotherapy. To add to the evidence, we present 2 novel cases of ICI exposure in pregnancy; 1 patient was treated for metastatic melanoma, and another for metastatic renal cell carcinoma. Table 2 summarizes the relevant details of each case report.

**CASE PRESENTATIONS**

**Case 1**

The patient is a 34-year-old female who presented with a skin lesion along the left thigh in 2017. Biopsy identified malignant melanoma with 1.48 mm thickness. Wide local excision with sentinel lymph node biopsy was performed the same year, showing no residual lesion at the primary melanoma site and no lymph node involvement (0/5). Genetic testing was performed given a positive family history of malignant melanoma in the patient’s mother and grandfather, with negative results. Dermatology follow-up was performed every 6 months. The medical history was otherwise noncontributory. She had 2 uncomplicated pregnancies in 2017 and 2019, which resulted in the vaginal births of healthy infants.

In 2020, a neck lump was noted on clinical assessment. Shortly after, the patient noted other lumps along the breasts and chest wall. Ultrasound identified 7 breast nodules and 5 other lesions in the chest wall. Abdominal ultrasound revealed an intrauterine pregnancy at 13 weeks and 6 days gestational age. Subsequent results of breast node biopsy confirmed metastatic melanoma. Magnetic resonance imaging (MRI) of the brain revealed multiple brain lesions (the largest measuring 1.6 cm), abdominal ultrasound showed lesions in the abdominal wall, and subcutaneous and computed tomography of the chest identified pulmonary metastasis and possible mediastinal nodes.

The treatment plan included stereotactic radiotherapy of the brain and neck and combination immunotherapy with anti-PD-1 and anti-CTLA-4 checkpoint inhibitors. The patient was referred for consultation with Maternal-Fetal Medicine for counseling and ongoing management of the pregnancy. Pregnancy care options were reviewed, including termination of pregnancy, considering the maternal burden of disease and limited data on the safety of most immunotherapy agents. The patient opted to continue the pregnancy. The options of proceeding with maternal imaging and treatment (immunotherapy, radiotherapy) during pregnancy versus proceeding with intentional preterm birth and delayed maternal treatment were presented to the patient. The patient opted to proceed with full maternal treatment during pregnancy with a plan for delivery consideration at or after 32 weeks gestational age. Timing was chosen to reduce complications of extreme prematurity, limit fetal exposure to 1 course of immunotherapy, and allow the patient time to recover from the initiation of treatment.

Gadolinium-enhanced MRI revealed over 12 brain lesions with potential meningeal spread. The radiotherapy approach was then modified to the whole brain and posterior neck with hippocampal sparing and was commenced at 24 weeks gestational age, with a final estimated fetal dose of 3.4 cGy.

Dual immunotherapy with ipilimumab 3 mg/kg and nivolumab 1 mg/kg was commenced at 27 weeks gestational age, and 1 course was given in pregnancy. One week following the dose, head computed tomography showed 9 intra-axial enhancing mass lesions, the largest measuring 1.4 cm. Additional imaging continued to show extensive metastatic disease, predating pregnancy. The clinical course was further complicated by pneumonia and transaminitis (aspartate aminotransferase elevation by 5-fold the reference range), prompting admission for in-patient investigations and management. All workup for obstetrical and secondary causes was negative, and transaminitis was attributed to grade 3 hepatitis in the context of immunotherapy. Liver enzymes remained elevated but stable, with a slow response to steroids. The patient was placed on 2 mg/kg of solumedrol, then upon discharge, was sent home on prednisone 112.5 mg. Following the patient’s discharge from the hospital, the prednisone was tapered gradually. Liver enzymes normalized 4 weeks into prednisone taper, and the patient was rechallenged with nivolumab 6 weeks into the taper. Pneumonia symptoms resolved following a single course of antibiotics.

Serial fetal ultrasounds showed normal growth and well-being and the absence of signs of placental or fetal metastasis. An elective cesarean delivery by patient request was performed at 31 weeks gestational age. The mode of delivery was based on the deterioration of maternal status and patient preference. Antenatal steroids were given for fetal lung maturation. The patient delivered a female infant weighing 1.69 kg, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The postpartum course was uneventful. The multidisciplinary care team recommended against breastfeeding considering the lack of data regarding the safety of immunotherapy agents and the manufacturers’ recommendations.
to refrain from breastfeeding 5 and 3 months after the last doses of nivolumab and ipilimumab, respectively. Placental pathology did not show evidence of metastatic disease. The infant was followed by the pediatric oncology team. The abdominal ultrasound of the neonate was normal, with no signs of hepatic mass. A small nevus was identified in the right leg and deemed benign. The infant remained in the neonatal intensive care unit after delivery for a short term because of early delivery but has no concerns related to maternal exposure to immunotherapy during gestation.

**Case 2**

A 33-year-old nulliparous female presented with left flank and back pain in 2018, renal calculi, and frank hematuria leading to the diagnosis of high-grade medullary renal cell carcinoma. Surgical treatment included cytoreductive left nephrectomy, splenectomy, distal pancreactectomy, and lymph node dissection, which was complicated by a renal vein thrombosis. Pulmonary metastases were detected 6 months after the initial diagnosis. The patient was treated with gemicitabine and cisplat in for 3 cycles. Subsequently, the patient developed lumbar pain and distal coagulation with low 

The pregnancy progressed without complication with the patient giving birth to an infant that showed normal development at birth. It is interesting to note that, our patient treated for metastatic melanoma is the first to receive treatment with dual checkpoint inhibitors during the third trimester of gestation. It is theoretically plausible that the steroids initiated for the treatment of hepatic toxicity shortly after the administration of dual immunotherapy with anti-CTLA-4 and anti-PD-1 could have had a protective effect against the adverse effects on pregnancy. Previous cases reporting fetal outcomes after exposure to dual checkpoint inhibitors in pregnancy have also reported favorable fetal outcomes, with no reported immune-related adverse events in the fetus upon exposure in the first trimester of gestation.2,3,5

Our second case report describes the maternal and fetal outcomes of a woman diagnosed with medullary renal cell carcinoma. This case is unique because all the previously identified cases in the literature describe patients diagnosed with metastatic melanoma. Our patient was treated with single-agent nivolumab at conception, which was discontinued upon discovering the pregnancy at 8 weeks gestation. Despite exposure to nivolumab in the first trimester, the patient gave birth to an infant that showed normal development at birth. There have been 3 previous reports of fetal outcomes after exposure to single-agent nivolumab therapy in pregnancy, 2 of which reported no immune-related adverse events in the fetus.1,6 As mentioned previously, Xu et al4 reported the development of congenital hypothyroidism. This immune-related adverse event was believed to have resulted from nivolumab exposure in the first trimester of pregnancy.

Both pregnancy and malignancy are risk factors for venous thromboembolism, so both of our patients received prophylactic anticoagulation. Importantly, our second patient (with a diagnosis of renal cell carcinoma) had a history of venous thromboembolism, which further prompted the use of prophylactic anticoagulation.

Our second patient requested NIPT for fetal aneuploidy screening. NIPT showed inconclusive results, presumably because apoptotic tumor DNA was released into the maternal circulation and was detected at the time of diagnosis. The patient gave birth to an infant that showed normal development at birth. The pregnancy was complications were minimal. The patient received treatment with dual checkpoint inhibitors during the third trimester of gestation. It is theoretically plausible that the steroids initiated for the treatment of hepatic toxicity shortly after the administration of dual immunotherapy with anti-CTLA-4 and anti-PD-1 could have had a protective effect against the adverse effects on pregnancy.

In conclusion, our case reports add to the growing body of evidence that favorable pregnancy outcomes may be achievable despite antenatal exposure to ICIs. Nevertheless, given the lack of data, we recommend that all patients undergoing immunotherapy treatment be counseled about dual contraceptive methods, which should be used both during treatment and for an established period after the cessation of treatment. Furthermore, we emphasize the importance of assembling a multidisciplinary care team, especially given the unique needs of a patient concurrently experiencing pregnancy and malignancy.

**DISCUSSION**

Contrary to what the animal experiments suggest, reports of anti-PD-1/PD-L1 and anti-CTLA-4 mAb exposure (notably nivolumab and ipilimumab) in pregnant patients have primarily resulted in favorable fetal outcomes with no developmental abnormalities. One exception is a newborn who presented with congenital hypothyroidism, which was thought to have resulted from maternal exposure to anti-PD-1 treatment.4

Including our patients, there are 8 reports of patients exposed to ICIs in pregnancy as described in the literature. Our first case report describes the maternal and fetal outcomes of a woman diagnosed with metastatic melanoma and is the fourth case that describes maternal treatment with dual checkpoint inhibitors (nivolumab and ipilimumab) in pregnancy. While maternal disease response was mixed during pregnancy, the fetus showed normal development at birth. It is interesting to note that, our patient treated for metastatic melanoma is the first to receive treatment with dual checkpoint inhibitors during the third trimester of gestation. It is theoretically plausible that the steroids initiated for the treatment of hepatic toxicity shortly after the administration of dual immunotherapy with anti-CTLA-4 and anti-PD-1 could have had a protective effect against the adverse effects on pregnancy. Previous cases reporting fetal outcomes after exposure to dual checkpoint inhibitors in pregnancy have also reported favorable fetal outcomes, with no reported immune-related adverse events in the fetus upon exposure in the first trimester of gestation.2,3,5

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CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

None reported. All authors have declared that there are no financial conflicts of interest with regard to this work.

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