

REVIEW

## Immune checkpoint inhibitor administration during pregnancy: a case series

A. Andrikopoulou, A. M. Korakiti, K. Apostolidou, M. A. Dimopoulos & F. Zagouri\*

Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece



Available online xxx

**Background:** Immune checkpoint inhibitors have been widely implemented in current clinical practice. Although cancer occurs in ~1 out of 1000 pregnancies, treatment remains challenging. Until now, limited data exist regarding immunotherapy administration during pregnancy. This systemic review aims to synthesize all available data from immunotherapy administration in pregnant women and evaluate the efficacy and safety of immunotherapy during pregnancy.

**Patients and methods:** Eligible studies were identified by a search of the PubMed Medline database and Food and Drug Administration Adverse Events Reporting System Public Dashboard for the period 1 January 2000 to 1 April 2021; the algorithm consisted of a predefined combination of the words ‘immunotherapy’, ‘cancer’ and ‘pregnancy’. PRISMA guidelines were applied in this study.

**Results:** Overall, seven articles (seven pregnancies, nine neonates) were retrieved. The mean duration of immunotherapy administration was 9.8 weeks [standard deviation (SD): 11.27; median: 7.0; range: 1-32]. In all cases specified, melanoma was the malignancy reported. The mean gestational age at delivery was 30.4 weeks (SD: 5.03; median: 32.0; range: 24-38), whereas the mean weight of neonates at delivery was 1267 g (SD: 412.0; median: 1400; range: 590-1701). Only one neonate was born term at 38 weeks of pregnancy (11.1%; 1/9). Complications during pregnancy were observed in 71.4% of cases: intrauterine growth restriction (three cases), HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) (one case), placental insufficiency (one case) and low fetal heart rate (one case). The mean progression-free survival and overall survival were 16.0 and 25.2 months, respectively.

**Conclusion:** The administration of immune checkpoint inhibitors during pregnancy is associated with increased incidence of pregnancy complications, prematurity and low birth weight. The administration of these regimens is not recommended during gestation. Whenever applied, close monitoring of the mother and the fetus is required.

**Key words:** immunotherapy, immune checkpoint inhibitors, pregnancy, cancer

### INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape in clinical oncology. The understanding of the underlying principles of tumor immunology has allowed the development of molecules that block cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathways and manipulate the immune system to reactivate the antitumor immune response. CTLA-4 binding reduces interleukin 2 (IL-2) production and T-cell proliferation, while PD-1 binding leads to T-cell depletion via altered T-cell receptor signaling.<sup>1</sup> Under normal circumstances, CTLA-4 and PD-1 enable self-tolerance that is frequently deactivated in

malignancy. Blockade of these pathways can effectively overcome the tumor-mediated inhibition of T-cell function.<sup>2</sup>

The incidence of cancer during pregnancy remains rather low, occurring in ~1 in 1000 pregnancies.<sup>3,4</sup> Treatment of cancer during pregnancy, however, remains challenging. Administration of chemotherapy during the first trimester has been associated with increased risk of spontaneous abortion, congenital malformations or even fetal death.<sup>5</sup> Although the administration of certain chemotherapeutic drugs seems to be safe, the risk of intrauterine growth restriction (IUGR) remains a concern.<sup>5,6</sup> There are no data regarding the administration of immunotherapy during pregnancy other than animal studies and case reports. Anti-PD-1 agents like nivolumab and pembrolizumab are categorized as pregnancy category D by the Food and Drug Administration (FDA), whereas anti-CTLA-4 antibody ipilimumab is pregnancy category C.<sup>7-9</sup> In animal studies, nivolumab administration during pregnancy resulted in spontaneous abortion and increased neonatal death in cynomolgus monkeys that received between 9 and 42 times

\*Correspondence to: Associate Prof Flora Zagouri, Medical School, National and Kapodistrian University of Athens, 80 Vasilissis Sofias Avenue, 11528 Athens, Greece. Tel: +30-21-0338-1554; Fax: +30-21-3216-2511  
E-mail: [florazagouri@yahoo.co.uk](mailto:florazagouri@yahoo.co.uk) (F. Zagouri).

2059-7029/© 2021 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

higher dose than the one administered in humans.<sup>7</sup> Consistently, CTLA-4 blockade caused abortion, stillbirth, premature delivery (with corresponding lower birth weight) and an increased incidence of infant mortality in animals treated with ipilimumab at a dose approximately 2.6 to 7.2 times the human exposure.<sup>9</sup>

We aim here to review all existing cases of exposure to immunotherapy during pregnancy. A retrospective evaluation of the existing cases will help to determine the effect of ICI administration during pregnancy on the mother and the fetus.

## METHODS

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol of this systematic review was submitted to the institutional review board of Alexandra General Hospital, Medical University of Athens, Greece, and is available upon request. Eligible articles were identified by a search of the Medline bibliographic database and the FDA Adverse Events Reporting System (FAERS) Public Dashboard for the period 1 January 2000 to 1 April 2021 (see Figure 1). The search strategy consisted of the following keywords: (neoplasms OR neoplasm OR cancer OR cancers OR carcinoma OR carcinomas) AND (pregnancy OR pregnant OR gestation) AND (immunotherapy OR immune checkpoint inhibitors OR nivolumab OR pembrolizumab OR avelumab OR durvalumab OR cemiplimab OR ipilimumab). Furthermore, we checked all the references of relevant reviews and eligible articles that our search retrieved so as to identify potentially additional eligible articles. All prospective and retrospective studies, as well as case reports, were considered eligible for this systematic review. Reviews of literature were not included, however we checked all the references of relevant reviews for eligible studies.<sup>10-12</sup> Language restrictions were applied (only articles in English were considered eligible).<sup>13-15</sup> While working separately, two researchers (AA and AMK) collected and analyzed data from each eligible study. In case of disagreement between the members of each pair, team consensus was obtained after consulting the principal designers of the study (FZ and MAD).

All studies investigating the administration of ICIs during pregnancy, no matter of sample size, were eligible. Articles where immunotherapy with interferon was administered were excluded from our study.<sup>16-18</sup> In addition, cases where immunotherapy was administered exclusively before the gestational period or postpartum were also excluded.<sup>19-22</sup> From each one of those studies, the following data were extracted: first author, year of publication, type of immunotherapy administered during pregnancy, type of malignancy, patient age at diagnosis, patient age at pregnancy, gestational age (GA) at immunotherapy administration, total dose administered, GA at delivery, way of delivery (Cesarean section, etc.), fetal outcome [prematurity, respiratory distress syndrome (RDS), congenital abnormalities etc.], weight at delivery, adverse effects of immunotherapy, maternal outcome, maternal immune-related adverse

events (AEs) before or during pregnancy, overall survival (OS) and progression-free survival (PFS) in months. PFS was defined as the time from immunotherapy initiation to time of disease recurrence. OS was defined as the time from immunotherapy initiation to death from any cause. In case of overlapping publications emerging from the same study, the larger size study was evaluated.

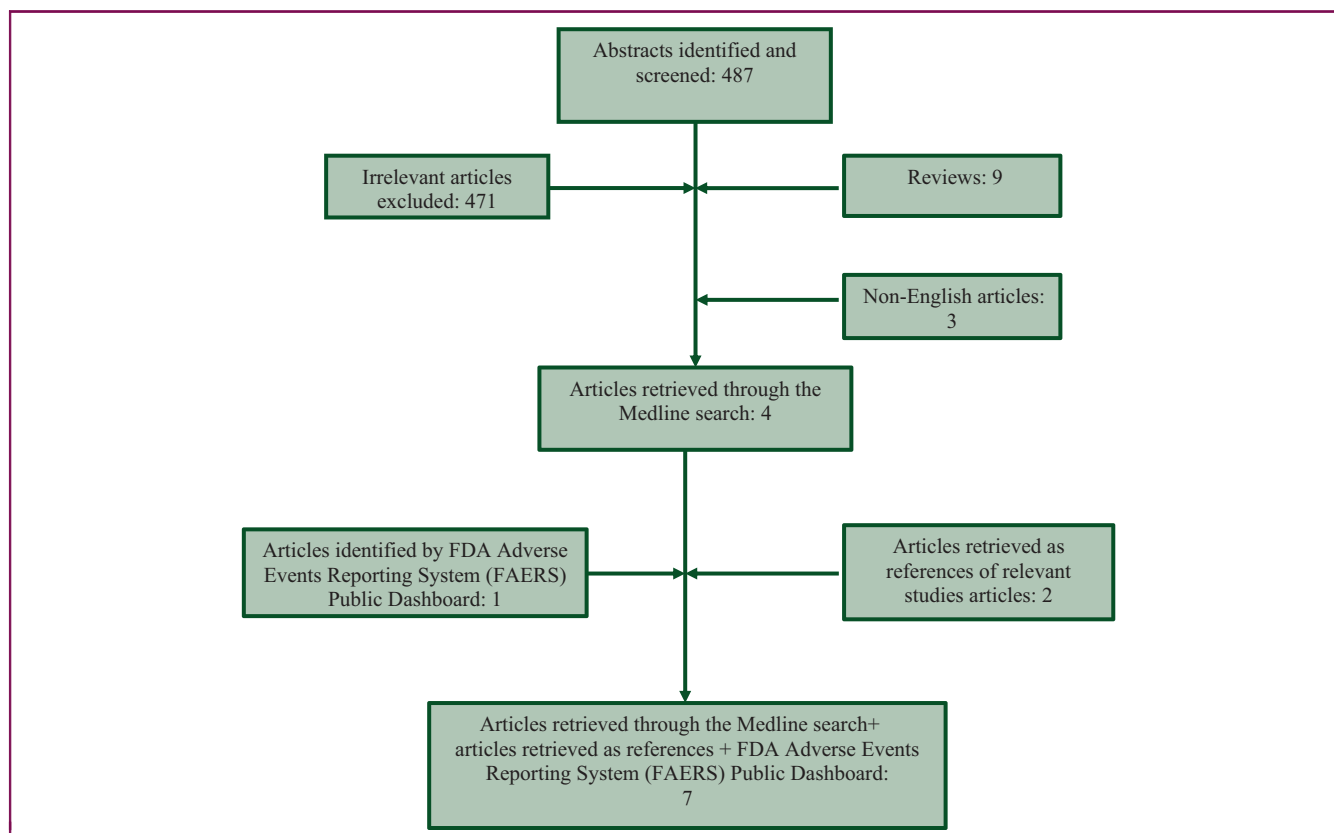
## RESULTS

Overall, 487 articles were identified and screened. After removal of 471 irrelevant articles, 9 reviews<sup>10-12,23-28</sup> and 3 non-English articles,<sup>13-15</sup> 4 studies were considered eligible for our review.<sup>29-32</sup> Having investigated the references of the relevant reviews and eligible articles, two more articles were added.<sup>33,34</sup> An additional search of the FAERS Public Dashboard<sup>35</sup> revealed one more eligible study.<sup>36</sup>

Detailed information of all eligible studies is provided in Table 1. The mean age of pregnant women at diagnosis was 26.9 years [standard deviation (SD): 5.31; median: 27.0; range 19-35],<sup>29-34,36</sup> whereas the mean age of cancer patients at pregnancy was 34.1 years (SD: 2.41; median: 34.0; range 32-39).<sup>29-34,36</sup> Among the immunotherapy regimens administered during pregnancy, nivolumab was administered as a single agent<sup>31,34</sup> or in combination with ipilimumab,<sup>29,30,32,36</sup> whereas there was one case of monotherapy with ipilimumab.<sup>33</sup> In all cases specified, melanoma was diagnosed,<sup>29-34,36</sup> whereas there was one case of uveal melanoma reported.<sup>34</sup> In all cases, immunotherapy was administered in the metastatic setting.<sup>29-34,36</sup> The mean duration of immunotherapy administration was 9.8 weeks (SD: 11.27; median: 7.0; range: 1-32).<sup>29-31,33,34,36</sup>

According to the data provided, two patients received four cycles of nivolumab/ipilimumab,<sup>30,32</sup> one patient received two cycles of nivolumab/ipilimumab combination,<sup>29</sup> one patient received one cycle of nivolumab/ipilimumab combination<sup>36</sup> whereas in one patient four cycles of ipilimumab were administered.<sup>33</sup> In four cases, immunotherapy had been initiated before pregnancy.<sup>30,31,33,34</sup> Five pregnancies were exposed to immunotherapy during the first trimester,<sup>30-34</sup> whereas two of them were exposed to immunotherapy exclusively during the second/third trimester.<sup>29,36</sup>

Pregnancy outcomes were described in all of the cases identified. Cesarean section was carried out in six out of seven pregnancies,<sup>29-32,34,36</sup> whereas vaginal delivery was carried out in one case.<sup>33</sup> In all cases specified, placental melanoma metastasis was not identified in the majority of cases (4/5)<sup>30,31,34,36</sup> and there was only one case of placental micrometastases at the maternal site.<sup>29</sup> The mean GA at delivery was 30.4 weeks (SD: 5.03; median: 32.0; range: 24-38),<sup>29-34,36</sup> whereas the mean weight of neonates at delivery was 1267 g (SD: 412.0; median: 1400; range: 590-1701).<sup>29-32,34</sup> Consistently, eight out of nine neonates were premature (88.9%)<sup>29-32,34,36</sup> and only one neonate was born term at 38 weeks of gestation.<sup>33</sup> In 3 cases (3/9) a completely healthy neonate was born,<sup>32-34</sup> while in the remaining cases (6/9)<sup>29-31,36</sup> the following conditions were



**Figure 1. Stages of the search strategy.**

FDA, Food and Drug Administration.

noted: RDS (two cases),<sup>29,36</sup> intraventricular hemorrhage grade II (one case),<sup>29</sup> retinopathy of prematurity grade II (one case),<sup>29</sup> congenital hypothyroidism (one case),<sup>31</sup> upper limb malformation (one case)<sup>34</sup> and severe combined immunodeficiency (SCID) (one case).<sup>36</sup>

AEs during pregnancy were observed in five out of seven cases: IUGR in three cases,<sup>30,31,34</sup> HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) in one case,<sup>34</sup> placental insufficiency in one case<sup>32</sup> and low fetal heart rate.<sup>32</sup> Immune-related AEs during pregnancy were reported in two cases: grade 1 diarrhea in one case<sup>33</sup> and immune-related hepatitis in another case<sup>32</sup> with increased bilirubin (grade 3), increased aspartate aminotransferase/alanine aminotransferase (grade 3) and increased gamma-glutamyl transferase (grade 4).

With regard to the maternal outcome, according to the data provided, the mean PFS was 16.0 months, whereas the mean OS was 25.2 months.<sup>29-34,36</sup> The qualitative interpretation of the individual eligible studies is provided below, in the discussion section.

## DISCUSSION

Treatment of cancer during pregnancy is a challenging condition that requires the careful weighing of disease progression against the risks to the fetus and the mother. There are limited data regarding the administration of immunotherapy during pregnancy that mainly emerge from animal studies. To our knowledge, this is the first review

summarizing all existing cases of immunotherapy administration during pregnancy reported in literature. We show here that there is an increased incidence of complication during pregnancy (71.4%), prematurity (88.9%) and low birth weight (1267 g) following immunotherapy administration during pregnancy, although the available information is scarce (see Figure 2).

Notably, the malignancy reported was melanoma in all cases. Malignant melanoma is one of the most common malignancies diagnosed during pregnancy along with cervical cancer, breast cancer, lymphomas and leukemias and accounts for 2.8 per 1000 deliveries.<sup>4</sup> Melanoma accounts for ~8% of malignant tumors diagnosed during pregnancy. A review of case reports reported an incidence of transplacental melanoma metastasis of 16.7% in patients with metastatic disease.<sup>37</sup> Metastasis to the placenta is rare, however, melanoma is the malignancy that metastasizes more frequently to the placenta. In our study, placental metastasis was reported in only one case (20%).<sup>29</sup>

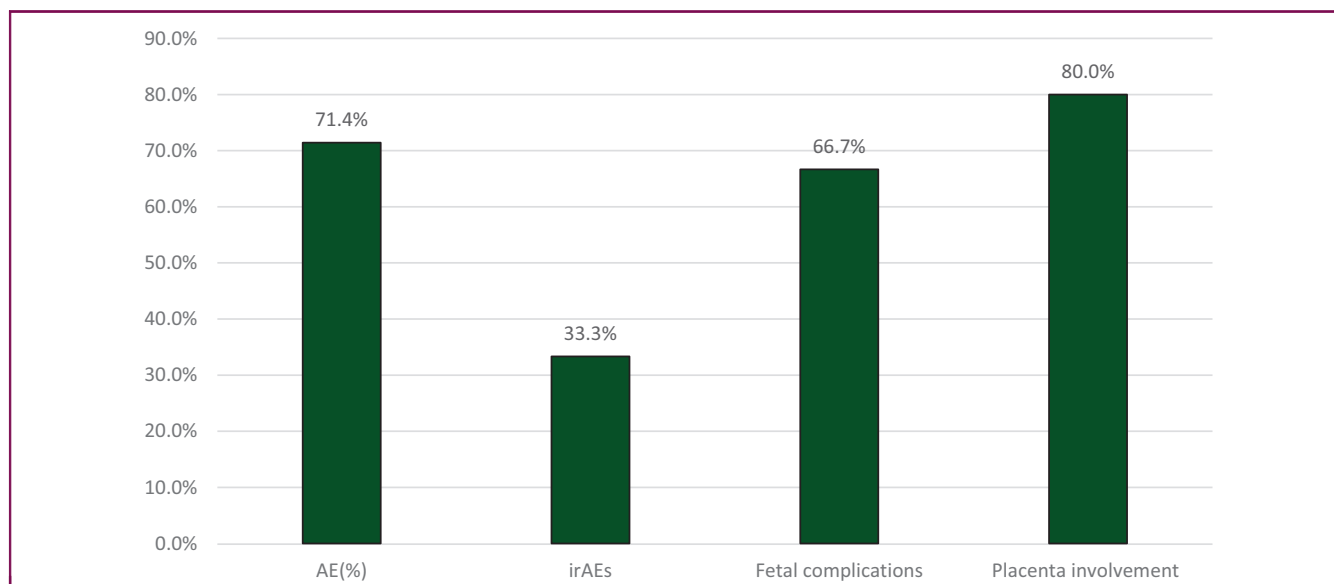
Since the fetus represents a foreign entity to the maternal immune system, it is necessary for the mother to develop an immune tolerance towards the fetus for the continuation of pregnancy. PD-1/PD-L1 interactions have been shown to play a key role in immunotolerance of the mother towards the paternal alloantigens of the fetus.<sup>38</sup> PD-L1 (B7-H1) is overexpressed in the syncytiotrophoblast and extravillous cytotrophoblasts in the human placenta.<sup>38</sup> PD-L1 is a negative regulator of the maternal alloimmune responses and blockade of this pathway could result in

**Table 1. Summary of case reports describing the administration of immunotherapy during pregnancy for cancer**

Author/date	Immunotherapy administered	Type of malignancy	Stage at pregnancy	Previous chemo/immunotherapy	Age at diagnosis	Age at pregnancy	GA at immunotherapy	Total dose administered	GA at delivery	Way of delivery	Placenta melanoma involvement	Weight at delivery
Mehta et al., 2018 <sup>33</sup>	Ipilimumab	Melanoma	IV (cutaneous in-transit, subcutaneous, nodal)	Vemurafenib	31	33	Before pregnancy-9th GA week	4 Cycles (3 mg/kg)	Full-term (>38th GA week)	Normal delivery	NR	NR
Menzer et al., 2018 <sup>29</sup>	Nivolumab, ipilimumab	Melanoma	IV (lung, pleura, lymph nodes, spine, liver and spleen)	NR	22	34	21st GA week-24th GA week	2 Cycles (nivolumab 1 mg/kg, ipilimumab 3 mg/kg)	24 + 2 GA week	Cesarean section	Yes (micro metastases at the maternal site)	590 g
Bucheit et al., 2020 <sup>30</sup>	Nivolumab, ipilimumab	Melanoma	IV (brain, breast, peritoneum, ovary)	Cisplatin, vinblastine, dacarbazine (CVD), interleukin 2 (IL-2), interferon Vemurafenib, cobimetinib, atezolizumab	27	32	Before pregnancy-delivery (32nd GA week)	4 Cycles of nivolumab 1 mg/kg, ipilimumab 3 mg/kg, then monotherapy with nivolumab 1 mg/kg every 3weeks	32nd GA week	Cesarean section	No	Twin A: 1530 g Twin B: 1700 g
Xu et al., 2019 <sup>31</sup>	Nivolumab	Melanoma	IV (lung, liver)	Ipilimumab, nivolumab	27	32	Before pregnancy-7th + 6 GA week	NR (nivolumab (3 mg/kg) twice weekly)	33rd GA week	Cesarean section	No	1400 g
Burotto et al., 2018 <sup>32</sup>	Nivolumab, ipilimumab	Melanoma	IV (breast, nodal, lung liver bone)	No	27	34	9th GA week- 2nd trimester	4 Cycles of nivolumab/ipilimumab followed by 1 cycle of nivolumab	32nd GA week	Cesarean section	NR	1640 g
Haiduk et al., 2021 <sup>34</sup>	Nivolumab	Uveal melanoma	IV (heart, lung)	No (radiotherapy, surgical resection of heart metastasis)	19	39	Before pregnancy-6th GA week	NR (240 mg nivolumab every 2 weeks)	30th GA week	Cesarean section	No	Twin A: 1055g Twin B: 950g
Niemi et al., 2017 <sup>36</sup>	Nivolumab, ipilimumab	Melanoma	IV (liver, lungs, chest wall, spleen, bone)	No	35	35	24 + 3 GA week	1 Cycle of nivolumab/ipilimumab	24 + 5 GA week	Cesarean section	No	NR
Author (continued)	Maternal irAE before pregnancy	Maternal irAE during pregnancy	AE during pregnancy	Fetal outcome	Maternal outcome	PFS	OS					
Mehta et al., 2018 <sup>33</sup>	G1 diarrhea	G1 diarrhea	None	No melanoma metastasis, Healthy at 2 years 9 months	PD during pregnancy (five new in-transit metastases), Initiation of pembrolizumab 1 month postpartum, PD to pembrolizumab 2 years later	7 months	>30 months					
Menzer et al., 2018 <sup>29</sup>	No	No	No IUGR, no melanoma metastasis to the fetus	Very premature, respiratory distress syndrome, intraventricular hemorrhage grade II on day 3 after birth, retinopathy of prematurity grade II. No signs of melanoma. At 6 months elevated tonus of the lower extremities/slight delay in motor development	Died 1 day postpartum (after 2 cycles of treatment)	1 month	1 month					

Bucheit et al., 2020 <sup>30</sup>	No	No	Twin A: IUGR (<10th percentile) Twin B: IUGR (<10th percentile)	Twin A: admission in neonatal intensive care unit for 30 days Twin B: admission in neonatal intensive care unit for 28 days	Generalized tonic-clonic seizure on day 1 postpartum. Treatment with dexamethasone and levetiracetam, monotherapy with nivolumab with no PD at 1 year	>12 months	>12 months
Xu et al., 2019 <sup>31</sup>	G3 GGT elevation, G2 rash, lymphocytic hypophysitis, bursitis, vitiligo	No	Moderate IUGR	Congenital hypothyroidism with a normally descended thyroid gland (due to immune-related thyroiditis?). Admission in neonatal intensive care unit for 5 weeks Healthy at 6 months follow-up	Complete response at 7 months postpartum	>27.25 months	>27.25 months
Buratto et al., 2018 <sup>32</sup>	No	Immune hepatitis with G3 bilirubin rise; G3 AST/ALT elevation; G4 GGT elevation	Placental insufficiency, low fetal heart rate	No melanoma metastasis, Apgar score 6/9 at 1 and 5 min, healthy at 11 months	Immune hepatitis/cholestasis postpartum and treatment with azathioprine and steroids, PD to immunotherapy. Underwent surgery and radiotherapy and started treatment with vemurafenib, PR to vemurafenib	6 months	>11 months
Haiduk et al., 2021 <sup>34</sup>	No (previous history of autoimmune hepatitis)	No	Twin A: IUGR after the 24th GA week Twin B: IUGR after the 24th GA HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count)	Twin A: healthy Twin B: upper limb malformation (strangulation by amniotic cord), healthy at 9 months postpartum	CR at nivolumab. Disease-free at 9 months postpartum	>19.25 months	>19.25 months
Niemi et al., 2017 <sup>36</sup>	No	NR	Preterm delivery	Respiratory distress syndrome, placed on ventilator, 'incomplete' testing for severe combined immunodeficiency (SCID)	NR	>0.07 months	>0.07 months

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; G, grade; GA, gestational age; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event; IUGR, intrauterine growth restriction; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.



**Figure 2. Complications of ICI administration during pregnancy.**

AE, adverse event; irAR, immune-related adverse event; ICI, immune checkpoint inhibitor.

enhanced fetal rejection. ICIs could theoretically result in an immune response against the fetus. Indeed, Guleria et al.<sup>38</sup> reported that treatment with anti-PD-L1 resulted in a five-fold increase in the rate of spontaneous resorption of allogeneic murine pregnancy from 18%-86%. Moreover, treatment with anti-PDL1 inhibitors resulted in expansion of Th1 effector cells.<sup>38</sup> Concerning the fact that a balance of Th1/Th2 cytokines is required for the outcome of a healthy pregnancy, expansion of alloreactive Th1 cells could prove to be deleterious for the pregnancy outcome.

In accordance with the expression of PD-L1 in trophoblasts, CTLA-4 is expressed in fetal tissues at the maternal-fetal interface.<sup>39</sup> In addition, CTLA-4 is expressed at a high rate in human T-regulatory cells (Tregs) and Tregs increase during pregnancy to promote maternal tolerance.<sup>40,41</sup> Anti-CTLA-4 ipilimumab depletes Tregs with membrane CTLA-4 expression via ADCC/ADCP (antibody-derived cell cytotoxicity/phagocytosis).<sup>41</sup> This depletion could abolish the Treg-mediated immunotolerance of the fetus. In the cynomolgus monkey DART study, the treatment of pregnant animals with ipilimumab was associated with adverse effects occurring primarily in the third trimester including higher abortion rates, premature delivery and higher incidence of infant mortality.<sup>28</sup> In animal studies, cynomolgus monkeys were given 2.6 to 7.2 times the human dose of 3 mg/kg beginning in the third trimester and were found to have dose-related increases in abortion, stillbirth, premature delivery and an increased incidence of mortality. In addition, developmental abnormalities were identified in the urogenital system of two infant monkeys exposed to 30 mg/kg of ipilimumab (7.2 times the human dose): one case of unilateral renal agenesis of the left kidney and ureter and one case of imperforate urethra.<sup>9</sup> As a result, ipilimumab is categorized as pregnancy category C by the FDA in the absence of adequate well-controlled human studies.<sup>9</sup>

Another concern about the administration of ICIs during pregnancy is the high incidence of immune-related AEs. Immune-related hypophysitis may lead to pituitary hormone abnormalities including impairment of follicle stimulating hormone and luteinizing hormone secretion. Immune-related hypophysitis is more commonly reported in patients treated with anti-CTLA-A inhibitors (0%-17%) than with PD-1 inhibitors nivolumab and pembrolizumab (0.5%-2.0%), whereas PD-L1 inhibitors rarely cause hypophysitis.<sup>42</sup> In our study, there were two cases of immune-related AEs during pregnancy. In addition, treatment of immune-related AEs requires the administration of corticoids and other immunosuppressive treatments that in theory could also affect the fetal outcome. Exposure to repetitive courses of antenatal glucocorticoids has been associated with fetal growth restriction, impairment of cerebral myelination, lung growth and hypothalamic–pituitary–adrenal axis and increased risk of neonatal hypoglycemia.<sup>43-45</sup>

Nivolumab and pembrolizumab are both immunoglobulin G4 (IgG4) antibodies that can be transferred across the placenta, potentially leading to immune-related AEs in the exposed fetus. Fetal IgG levels remain low during the first two trimesters of pregnancy and typically increase during the third trimester so that the levels of IgG4 in the fetus are similar to those in the maternal circulation.<sup>28</sup> Therefore, both nivolumab and pembrolizumab have the potential to be transmitted from the mother to the developing fetus and thus theoretically to cause immune-related AEs in the fetus. In our study, there was one case of congenital hypothyroidism reported with a normally descended thyroid gland. Such a malformation could be a result of immune-related thyroiditis of the fetus. It could be thus postulated that the fetus is minimally exposed during organogenesis while this exposure to IgG4 antibodies would increase during the third trimester of pregnancy.

At this time, anti-PD-1 agents are categorized as pregnancy category D by the FDA.<sup>7,8</sup> Animal reproduction studies have not been conducted with anti-PD-1 pembrolizumab to evaluate its effect on reproduction and fetal development. The estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20% in the USA.<sup>7</sup> In contrast, nivolumab has been evaluated in cynomolgus monkeys. Nivolumab was administered twice weekly from the onset of organogenesis through delivery at a dose between 9 and 42 times higher than the one administered in humans.<sup>8</sup> Treatment with nivolumab resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death in monkeys. Of note, there were no apparent malformations and no effects on neurobehavioral, immunological or clinical pathology parameters throughout the 6-month post-natal period in babies of cynomolgus monkeys that received nivolumab.

A thorough search of the FAERS Public Dashboard was conducted to evaluate the registered cases of administration of anti-PD-1/anti-PD-L1 or anti-CTLA-4 during pregnancy. The most frequently used ICIs (nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab) were evaluated. Until now, there are 62 cases of nivolumab administration during pregnancy, 38 cases of ipilimumab administration and 7 cases of pembrolizumab administration registered in the database.<sup>46</sup> The most commonly reported complications are spontaneous abortion, fetal growth restriction, premature delivery, fetal distress syndrome and a few cases of congenital abnormalities (congenital hypothyroidism, congenital hand malformation). In most cases a Cesarean section was carried out and a premature neonate was delivered.<sup>46</sup>

It is well known that human fetuses are exposed to maternal IgG antibodies via the neonatal Fc receptor.<sup>47</sup> In addition, IgG1 subclass is transported most effectively, followed by IgG4, IgG3 and finally IgG2 with the least transport. Fetal IgG levels remain low during the first two trimesters of pregnancy and typically rise during the third trimester, so that the levels of IgG4 in the fetus are similar to or exceed those in the maternal circulation.<sup>47</sup> Nivolumab and pembrolizumab are both IgG4 antibodies. Given the low to very low exposure to maternal antibodies during organogenesis, it would seem unlikely that ICIs could have a detrimental impact on the embryo during early pregnancy. Consequently, patients conceiving while on treatment with ICIs should not be encouraged to abort, as the fetus would be barely exposed. According to the FDA instructions, women should be advised to use effective contraception during treatment and for at least 5, 4 and 3 months after the last dose of nivolumab, pembrolizumab and ipilimumab respectively.<sup>7-9</sup>

As previously mentioned, the risk of IgG antibody transfer is higher during the third trimester of pregnancy. In addition, melanoma is one of the most common malignancies diagnosed during pregnancy. There is evidence that increased risk of transplacental melanoma transmission occurs beyond 36 weeks of gestation.<sup>31</sup> It could thus be

speculated that gestation would be at greater risk during the third trimester. The management of patients with controlled disease should be based on a consensus including different medical specialties: medical oncologists, obstetricians and neonatologists. Clinicians, however, could consider elective delivery at 34-36 weeks rather than waiting to term to avoid maximum exposure of the fetus.

## CONCLUSION

While immunotherapy is not complicated by the teratogenic effects of chemotherapy, it could deactivate maternal immunotolerance leading to miscarriages, impaired fetal growth or immune-related adverse effects in the fetus or the mother. However, this causative link is still unclear, since other factors could potentially affect the pregnancy outcome, such as the advanced stage of disease. Consequently, there is an unmet need for clinical trials evaluating the real incidence of these data, although such an endeavor would confront ethical and human rights restrictions. For the time being, the utilization of ICIs during pregnancy is not recommended. A multidisciplinary approach and close monitoring of the pregnancy are of high importance whenever these agents are used during pregnancy.

## ACKNOWLEDGEMENTS

Not applicable.

## FUNDING

None declared.

## DISCLOSURE

MAD has received honoraria from participation in advisory boards from Amgen, Bristol Myers Squibb, Celgene, Janssen, Takeda. FZ has received honoraria for lectures and has served in an advisory role for AstraZeneca, Eli-Lilly, Merck, Novartis, Pfizer and Roche. The remaining authors have declared no conflicts of interest.

## DATA SHARING

Data supporting our findings can be found in PubMed bibliographical database and FDA Adverse Events Reporting System (FAERS) Public Dashboard.

## REFERENCES

- Li X, Shao C, Shi Y, Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. *J Hematol Oncol.* 2018;11(1):31.
- Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res.* 2019;38(1):255.
- de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol.* 2018;19(3):337-346.
- Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist.* 2002;7(4):279-287.
- Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol.* 2004;5(5):283-291.

6. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol*. 2010;28(4):683-689.
7. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/125514s071s090lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s071s090lbl.pdf). Accessed May 14, 2021.
8. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/125554s082lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s082lbl.pdf). Accessed May 14, 2021.
9. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/125377s110lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s110lbl.pdf). Accessed May 14, 2021.
10. Rzeniewicz K, Larkin J, Menzies AM, Turajlic S. Immunotherapy use outside clinical trial populations: never say never? *Ann Oncol*. 2021;32:866-880.
11. Hepner A, Negrini D, Hase EA, et al. Cancer during pregnancy: the oncologist overview. *World J Oncol*. 2019;10(1):28-34.
12. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. *Cancer*. 2017;123(11):1904-1911.
13. Benardete-Harari DN, Kershenovich-Gersson J, Meraz-Ávila D, Galnares-Olalde JA, Olaya-Guzmán EJ. Use of chemotherapy during pregnancy. *Rev Med Inst Mex Seguro Soc*. 2016;54(6):752-758.
14. Karbowski B, Jackisch C. Malignant melanoma and pregnancy. *Z Geburtshilfe Neonatol*. 2000;204(4):158-161.
15. Jasaitiene D, Valiukeviciene S, Makstiene J, Juodzbaliene EB. Metastatic amelanotic nodular melanoma during pregnancy. *Medicina (Kaunas)*. 2008;44(6):467-471.
16. Ustaalioglu BBO, Gumus M, Ünal A, et al. Malignancies diagnosed during pregnancy and treated with chemotherapy or other modalities (review of 27 cases). *Int J Gynecol Cancer*. 2010;20(5):698-703.
17. Egberts F, Lischner S, Russo P, Kampen WU, Hauschild A. Diagnostische und therapeutische maßnahmen in der behandlung des malignen melanoms während der schwangerschaft: Risiko für den fetus? Fallbericht und literatur-überblick. *J Dtsch Dermatol Ges*. 2006;4(9):717-720.
18. Gottschalk N, Jacobs VR, Hein R, Fischer T, Schneider KTM, Pildner Von Steinburg S. Advanced metastatic melanoma during pregnancy: a multidisciplinary challenge. *Onkologie*. 2009;32(12):748-751.
19. Bolze PA, You B, Lotz JP, et al. Successful pregnancy in a cancer patient previously cured of a gestational trophoblastic tumor by immunotherapy. *Ann Oncol*. 2020;31(6):823-825.
20. Nai GA, Bazan A, Rocha CA, Nagy JS, Campos IT. Postpartum genital melanoma - a case report. *Rev Bras Ginecol Obstet*. 2018;40(3):163-167.
21. Soares A, dos Santos J, Silva A, Magalhães H, Estevinho F, Sottomayor C. Treatment of lung cancer during pregnancy. *Pulmonology*. 2020;26(5):314-317.
22. Erdmann C, Zicholl S, Bröckling S, et al. A 33 year old pregnant women with an adenoneuroendocrine carcinoma (MANEC) of the cervix uteri. *Oncol Res Treat*. 2017;40(3):232-233.
23. Azim HA, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: hematological tumors. *Cancer Treat Rev*. 2010;36(2):110-121.
24. Azim HA, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: solid tumors. *Cancer Treat Rev*. 2010;36(2):101-109.
25. Poggio F, Tagliamento M, Pirrone C, et al. Update on the management of breast cancer during pregnancy. *Cancers (Basel)*. 2020;12(12):1-17.
26. Flint TR, Jones JO, Ferrer M, Colucci F, Janowitz T. A comparative analysis of immune privilege in pregnancy and cancer in the context of checkpoint blockade immunotherapy. *Semin Oncol*. 2018;45(3):170-175.
27. Grunewald S, Jank A. Neue dermatologische systemtherapien bei kinderwunsch, schwangerschaft und stillzeit. *J Dtsch Dermatol Ges*. 2015;13(4):277-292.
28. Poulet FM, Wolf JJ, Herzyk DJ, DeGeorge JJ. An evaluation of the impact of PD-1 pathway blockade on reproductive safety of therapeutic PD-1 inhibitors. *Birth Defects Res B Dev Reprod Toxicol*. 2016;107(2):108-119.
29. Menzer C, Beedgen B, Rom J, et al. Immunotherapy with ipilimumab plus nivolumab in a stage IV melanoma patient during pregnancy. *Eur J Cancer*. 2018;104:239-242.
30. Bucheit AD, Hardy JT, Szender JB, Glietza Oliva IC. Conception and viable twin pregnancy in a patient with metastatic melanoma while treated with CTLA-4 and PD-1 checkpoint inhibition. *Melanoma Res*. 2020;30(4):423-425.
31. Xu W, Moor RJ, Walpole ET, Atkinson VG. Pregnancy with successful foetal and maternal outcome in a melanoma patient treated with nivolumab in the first trimester: case report and review of the literature. *Melanoma Res*. 2019;29(3):333-337.
32. Burotto M, Gormaz JG, Samtani S, et al. Viable pregnancy in a patient with metastatic melanoma treated with double checkpoint immunotherapy. *Semin Oncol*. 2018;45(3):164-169.
33. Mehta A, Kim KB, Minor DR. Case report of a pregnancy during ipilimumab therapy. *J Glob Oncol*. 2018;4:1-3.
34. Haiduk J, Ziemer M. Pregnancy in a patient with metastatic uveal melanoma treated with nivolumab. *J Dtsch Dermatol Ges*. 2021;19(5):762-765.
35. FDA Adverse Events Reporting System (FAERS) Public Dashboard - FDA Adverse Events Reporting System (FAERS) Public Dashboard | Sheets - Qlik Sense. Available at <https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis>. Accessed May 14, 2021.
36. Niemi A, Foeller ME, Yeaton-Massey A, Fan AC, Winn VD, Hintz SR. Preterm birth after treatment of maternal metastatic melanoma with immunotherapeutics. In: *Western Medical Research Conference 2017 (Formerly Western Regional Meeting) Camel, California, January 26-28, 2017*. Journal of Investigative Medicine; 2017. Available at <https://jim.bmj.com/content/65/1/254>. Accessed May 14, 2021.
37. Mendizábal E, De León-Luis J, Gómez-Hidalgo NR, et al. Maternal and perinatal outcomes in pregnancy-associated melanoma. Report of two cases and a systematic literature review. *Eur J Obstet Gynecol Reprod Biol*. 2017;214:131-139.
38. Guleria I, Khosroshahi A, Ansari MJ, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med*. 2005;202(2):231-237.
39. Kaufman KA, Bowen JA, Tsai AF, Bluestone JA, Hunt JS, Ober C. The CTLA-4 gene is expressed in placental fibroblasts. *Mol Hum Reprod*. 1999;5(1):84-87.
40. Selby MJ, Engelhardt JJ, Quigley M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. *Cancer Immunol Res*. 2013;1(1):32-42.
41. Sobhani N, Tardiel-Cyril DR, Davtyan A, Generali D, Roudi R, Li Y. CTLA-4 in regulatory T cells for cancer immunotherapy. *Cancers (Basel)*. 2021;13(6):1-18.
42. Mortensen MJ, Oatman O, Azadi A, Fonkem E, Yuen KC. An update on immune checkpoint inhibitor-related hypophysitis. *US Endocrinol*. 2020;16(2):117-124.
43. Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med*. 2007;357(12):1190-1198.
44. Committee on Obstetric Practice. Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):e102-e109.
45. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. *BMJ*. 2016;355:i5044.
46. FDA Adverse Events Reporting System (FAERS) Public Dashboard | Sheets - Qlik Sense. Available at <https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis>. Accessed May 14, 2021.
47. Pentšuk N, Van Der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth Defects Res B Dev Reprod Toxicol*. 2009;86(4):328-344.