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LETTER TO EDITOR

Management of ADA-Deficient SCID Patient on Adagen During Pregnancy

Marissa Shams [1,2] · Lisa Kobrynski [1,3]

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Abbreviations

ADA	Adenosine deaminase
SCID	Severe combined immune deficiency
ADA-SCID	Adenosine deaminase severe combined immune deficiency

To the Editor:

We describe the management of a patient with ADA-deficient Severe Combined Immune Deficiency maintained on PEG-ADA treatment throughout her pregnancy. ADA-deficient SCID (ADA-SCID) is rare but accounts for approximately 15% of all SCID cases. Prior to the mid-1980s, few children with this diagnosis survived into adulthood. As a result of improved outcomes with definitive treatment such as hematopoietic cell transplant (HCT) and now gene therapy, few patients remain on long-term therapy with weekly PEG-ADA enzyme replacement alone. It is well known that increases in maternal plasma volume during gestation can cause physiologic dilution of hematologic and immunologic cell types and proteins [1]. Maternal blood volume increases by approximately 40–50% beginning at week 8 of gestation, peaking at week 32 [1]. Given the larger volume of blood distribution and decrease in serum albumin concentration, pregnant patients may require higher maintenance doses of medication to ensure therapeutic plasma concentrations [1]. There is also evidence that the maternal T cell response shifts in pregnancy to a more robust Th2 response rather than Th1, which may explain some autoimmune disease remission and increased susceptibility to influenza infections [2–4]. However, few recommendations exist to direct the care of pregnant patients with non-humoral immune deficiency much less those on current treatment with PEG-ADA. Knowledge detailing the management of ADA-SCID patients on PEG-ADA replacement during pregnancy is valuable to clinical immunologists.

A 27-year-old female with ADA-SCID on weekly PEG-ADA was followed before and throughout 9 months of pregnancy. Prior to pregnancy, she was well on weekly PEG-ADA (1500 IU/week) intramuscular injections. She had normal serum immunoglobulins (Igs) and did not require gammaglobulin replacement or prophylactic antibiotics. PEG-ADA was continued during pregnancy at her pre-pregnancy dosage. She was seen in clinic monthly for examination with laboratory assessment including complete blood cell counts with differential, lymphocyte flow cytometry, serum immunoglobulin (Ig) assessment, and dose adequacy assessment with red blood cell dAXP levels performed by Dr. Michael Hershfield (Duke University) (Table 1).

No issues were noted during the first trimester, including infection or abnormal laboratory studies. However, beginning early in the second trimester (week 16), she was started on Trimethoprim-Sulfamethoxazole prophylaxis three times per week as a result of dropping CD4 counts [185 cells/mm^3 (N *405-2178*)]. There was also a decline in lymphocyte proliferative responses to recall antigens (Candida) but responses to mitogens (PHA, ConA, and Pokeweed Mitogen) were preserved. Given her diagnosis of SCID, she was referred by her primary obstetrician to high-risk obstetrics-gynecology where she was diagnosed with gestational hypertension and pre-eclampsia and was started on anti-hypertensive therapy with methyldopa on week 16, subsequently changed to labetalol on week 22 given persistently elevated blood pressure. At her immunology follow-up the same week, laboratory

✉ Marissa Shams
marissa.reiter.shams@emory.edu

[1] Emory University School of Medicine, Atlanta, GA, USA

[2] The Emory Clinic, Atlanta, GA, USA

[3] Children's Healthcare of Atlanta, Atlanta, GA, USA

Table 1 Laboratory data

Weeks of gestation	Baseline (pre-partum)	8	11	16	22	32	33	2 weeks (post-partum)	6 months (post-partum)
Abs CD4+									
405–2178 cells	535	498	229	185	272	378	272	252	358
IgG									
694–1618 g/dl	839	767	705	717	621	589	1150	881	1200
dAXP									
< 0.002 mmol/ml/RBC	0.004	–	0.000	0.015	0.004	–	0.027	–	0.047
Plasma ADA level									
< 0.5 mmol/h/ml	35.80	–	30.48	17.58	18.22	–	17.23	–	17.90
Serum albumin (g/dl)	3.9	–	–	–	–	2.9	3.4	–	4.3
Hemoglobin (g/dl)	13.5	13.2	12.8	12.5	–	12.9	11.3	12.3	14.3

assessment revealed reduced serum Igs and gammaglobulin replacement therapy was recommended. She reported a traumatic history of gammaglobulin replacement in early childhood due to venous access issues and subsequently refused treatment despite strong provider encouragement. As hypogammaglobulinemia persisted into the third trimester, due to concerns for potential effects of hypogammaglobulinemia on the fetus, she reluctantly agreed to begin intravenous gammaglobulin therapy (IVIG). She was scheduled to have 3 monthly infusions prior to her due date. She received her first infusion at week 32. Approximately, 2 weeks after her infusion, she was directly admitted to the obstetrics service for further monitoring of pre-eclampsia after elevated liver enzymes, urinary protein and oligohydramnios were noted at her obstetrics visit. Upon admission, she was treated with magnesium infusion to delay preterm labor and prevent sequelae associated with pre-eclampsia. On week 34 + 2 days, she had spontaneous vaginal delivery of a baby girl (Apgar 8, 9). It is likely that her pre-existing preeclampsia combined with oligohydramnios precipitated labor. The baby was admitted to the NICU for 8 days because of neonatal jaundice and temperature dysregulation but was otherwise normal. Newborn CBC and differential were normal without lymphopenia. Unfortunately, at this time, newborn screening was not in place in the state and there is no assessment of her TREC value. The baby was discharged home at age 8 days of age.

Post-partum, the patient continued on IVIG monthly throughout the winter given persistently low serum IgG values. However, she ultimately discontinued her infusions as a result of insurance changes after her 6th infusion. She remained on TMP-SMX prophylaxis for 5 months but ultimately self-discontinued after development of upper respiratory infection requiring treatment with Amoxicillin-Clavulinic acid, per her primary care physician as she was concerned regarding polypharmacy.

Currently, our patient remains well on her pre-pregnancy dose of PEG-ADA without a need for prophylactic antibiotics or IVIG. T cell counts have improved and sIg levels have normalized.

Progressive lymphopenia and hypogammaglobulinemia may occur secondary to effects of immune changes in pregnancy, fluid volume shifts, but little is known about changes to PEG-ADA metabolism. There are few previous reports of PEG-ADA use during pregnancy. In our case, we speculate that the drop in T cells and sIg, with an increase in dAXP (Table 1), likely reflects decreased serum levels of ADA, possibly as a result of increased blood volume diluting serum ADA concentrations [4]. The formation of inhibitory anti-ADA IgG antibodies, which have been reported to reduce efficacy of PEG-ADA [5], was assessed via ELISA and levels were not significant. The absence of placental ADA may have led to elevated placental adenosine contributing to this patient's complicated obstetric course. A previous study by Giorgi et al. demonstrated that plasma ADA activity was increased in patients with preeclampsia in comparison with normotensive pregnant controls with the authors concluding that degradation of adenosine by ADA and subsequent accumulation of uric acid contribute to the systemic inflammatory response noted in precelampsia [6]. Another study demonstrated that chronically elevated placental adenosine was associated with the development of preeclampsia symptoms; notably, hypertension and proteinuria in mice and humans with elevated adenosine levels correlated with preeclampsia severity [7].

There is only one previous case report detailing the care of a 24-year-old ADA-deficient patient treated throughout pregnancy with PEG-ADA. This patient also required TMP-SMX prophylaxis for pneumocystis and IVIG use of 10 g/month [8] and during her second trimester had a reduction in her lymphocyte count with decreased ADA activity [8]. Since she remained well without infection or the development of pre-eclampsia, her PEG-ADA dosage was not increased. She underwent planned cesarean section at 39 weeks for breech presentation without any other abnormality or issue reported [8].

As regimens for management of ADA-SCID continue to improve, more immunologists may manage the care of these patients during pregnancy. A new ADA formulation, elapegademase Ivir, was just approved by the FDA. Few

guidelines detail the management of ADA-SCID patients during pregnancy. Pregnant PIDD patients require frequent assessment to detect a decline in immune function and increased infection, and ADA-deficient SCID patients on enzyme replacement require regular monitoring of adenosine levels to gauge the adequacy of the PEG-ADA replacement to ensure the health of the mother and baby.

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Compliance with Ethical Standards

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

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