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CORRESPONDENCE

Eplerenone levels in maternal serum, cord blood, and breast milk during pregnancy and lactation

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Hypertensive disorders affect ~10% of all pregnant women and are leading causes of maternal and perinatal mortality and morbidity [1]. Primary aldosteronism (PA) is currently considered one of the most common causes of secondary hypertension and has an estimated prevalence of ~3–6% among patients with hypertension [2, 3] and ~20% in patients with severe hypertension [4]. PA is characterized by autonomous aldosterone production with suppressed renin levels, either involving one adrenal gland (mostly due to an aldosterone-producing adenoma) or both adrenal glands. Choices for antihypertensive therapy in pregnant women with hypertension are limited. Unfortunately, spironolactone has been shown to have an adverse effect on the fetus in animal studies. There are no adequately controlled studies in humans. Furthermore, the potent antiandrogenic effects of spironolactone have the potential to cause ambiguous genitalia in male fetuses [5].

Unlike spironolactone, the selective aldosterone blocker eplerenone is licensed for use in individuals with hypertension and heart failure after myocardial infarction [6]. Eplerenone has fewer antiandrogenic effects, such as gynecomastia, mastalgia, feminization, and impotence [7]. Eplerenone has the potential to be a safer option than spironolactone. Although there are no adequately controlled studies in pregnant women, no adverse or teratogenic developmental effects were observed in pregnant animals receiving eplerenone during organogenesis at doses up to 32 times the therapeutic dose of 100 mg/day in humans [6]. Furthermore, one case report described an uneventful pregnancy in a woman treated with eplerenone for an aldosterone-producing adenoma. She delivered a healthy male infant who did not have any adverse effects during a follow-up of 2 years [8]. In addition, eplerenone was reported to be safe and effective in pregnant women with Gitelman syndrome [9] or diastolic heart failure [10]. Although there are some data about the safety of eplerenone in pregnant or lactating women, there is no published information about placental transfer of eplerenone in humans. Regarding the safety of breastfeeding during eplerenone treatment, preclinical data show that eplerenone is detectable in rat breast milk [6]. However, there are no data regarding eplerenone transfer into human breast milk. In this case report, we discuss the safety of eplerenone with reference to drug concentrations in cord blood, maternal serum, and breast milk.

A 44-year-old woman with PA weighing 63 kg became pregnant with her second child. She was diagnosed with early-onset preeclampsia during her first pregnancy, and she delivered a female infant weighing 1205 g during gestational week 30 via cesarean section. Thus, in her second pregnancy, 81 mg of low-dose aspirin was started at gestational week 11 to prevent the development of preeclampsia. Until gestational week 8, she received amlodipine at a dose of 10 mg daily. Eplerenone was also administered for only one week from gestational week 8. Due to elevated blood pressure (BP) during gestational week 25, amlodipine was converted to combination therapy consisting of nifedipine 40 mg twice daily and eplerenone 50 mg once daily (0.79 mg/kg/day). After the dose of nifedipine was increased to 60 mg twice daily and methyldopa 250 mg was added as needed, her systolic BP was controlled between 100 and 120 mmHg, and her diastolic

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Table 1 Eplerenone concentrations in serum and breast milk samples after administration of oral eplerenone 50 mg

Postpartum day	Maternal serum		Umbilical cord blood		Breast milk	
	Time after EPL dose (hours)	EPL concentration (ng/mL)	Time after EPL dose (hours)	EPL concentration (ng/mL)	Time after EPL dose (hours)	EPL concentration (ng/mL)
−1	1.3	505.2				
0	3.9	309.5	3.9	209.7		
1	22.9	1.0				
6	143.7	0.0				
7					1.0	0.0
					1.5	104.1
					11.5	61.3
35					1.0	130.2
					4.0	161.2
					6.5	55.8
					13.5	6.0
					18.5	0.7
					22.0	0.3
36	17.8	8.4				

EPL eplerenone

BP was controlled to 60–70 mmHg at home. During gestational week 38, a healthy male infant weighing 2918 g was born by cesarean section. Superimposed preeclampsia did not develop during her second pregnancy. During a 3-month lactation period, the infant was partially breastfed, with over 50% of nutrition derived from breastfeeding. The infant in this case demonstrated normal developmental progress and had no detectable drug-related adverse effects at the 1-month or 3-month postpartum health checkups.

To evaluate eplerenone exposure in utero and during infancy, maternal serum samples were collected after oral eplerenone 50 mg was administered. Umbilical cord blood was collected after delivery, and the serum was immediately separated by ultracentrifugation. Breast milk samples were collected several times after eplerenone administration and stored below –20 °C until analysis. The timing of sample collection after eplerenone administration is presented in Table 1. Eplerenone in serum and breast milk samples was determined using a modified version of a previously validated method based on liquid chromatography tandem mass spectrometry. This study was approved by the ethics committee of the National Center for Child Health and Development. The participant provided written informed consent.

Eplerenone concentrations in maternal serum were 505.2 ng/mL at 1.3 h after the last eplerenone dose and 309.5 ng/mL at delivery (3.9 h after the last dose). The eplerenone concentration in cord blood collected immediately after delivery (3.9 h after the last dose) was 209.7 ng/mL, which was 67.8% of the level in maternal serum. At 22.9 h after the last dose, the concentration of eplerenone decreased to 1.0 ng/mL.

In breast milk, eplerenone concentrations at 1.0, 1.5, and 11.5 h after the last dose on postpartum day 7 were 0.0, 104.1, and 61.3 ng/mL, respectively. On postpartum day 35, eplerenone concentrations at 1.0, 4.0, 6.5, 13.5, 18.5, and 22.0 h after the last dose were 130.2, 161.2, 55.8, 6.0, 0.7, and 0.3 ng/mL, respectively (Table 1). The calculated daily dose of eplerenone ingested by the infant via breast milk, based on the maximum detected eplerenone concentration in breast milk (161.2 ng/mL) and average breast milk intake (150 mL/kg/day), was 0.024 mg/kg/day; this was low compared to the weight-adjusted therapeutic dose of eplerenone for adults (50–100 mg once daily). The relative infant dose via breast milk based on the maternal daily dose was 3.0%, which was higher than that of labetalol (0.004%) [11], methyldopa (0.01%) [12], nifedipine (0.1%) [13], benazepril (0.1%) [14], enalapril (0.27%) [15] and captopril (1.0%) [16] and was the same level as that of amlodipine (4.2%) [17].

To the best of our knowledge, this is the first report describing the transfer of eplerenone across the placenta and into breast milk. In our case, eplerenone was detected in cord blood and breast milk. Although the patient received eplerenone in early pregnancy, no birth defects were found in her infant. The dose of eplerenone consumed by the infant via breastmilk was less than 10%, and this level was considered to be acceptable [18]. Further studies are needed

to evaluate potential harmful effects following exposure to eplerenone in utero and during breastfeeding.

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Compliance with ethical standards

Conflict of interest AM has received research grants from Astellas Pharma, Inc. and Chugai Pharmaceutical Co., Ltd. and lecture fees from Astellas Pharma, Inc., Chugai Pharmaceutical Co., Ltd., and Bristol-Myers KK. All other authors declare no conflicts of interest.

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