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Acid-Base and Electrolyte Teaching Case

Approach to the Diagnosis and Treatment of Hyponatremia in Pregnancy

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Hyponatremia is the most commonly encountered electrolyte abnormality. Severe hyponatremia in pregnancy poses diagnostic and therapeutic challenges. Pregnancy involves changes in physiology that affect water and sodium homeostasis. Knowledge of these complex physiologic alterations during pregnancy is critical to managing dysnatremias in pregnancy. This teaching case describes a woman with chronic hyponatremia who presented during pregnancy with worsening hyponatremia. She had an activating vasopressin receptor mutation, which was passed on to her child, and her diagnostic workup is described.
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INDEX WORDS: Hyponatremia; euvolemic hypotonic hyponatremia; sodium; syndrome of inappropriate antidiuretic hormone secretion (SIADH); pregnancy; vasopressin receptor; arginine vasopressin receptor 2 (AVPR2); R137C.

INTRODUCTION

Abnormalities in sodium and water handling are common in pregnancy. The abnormalities in water metabolism may lead to hyponatremia, which usually is mild in degree: serum sodium concentration $>$ 130 mEq/L. Evaluation for other causes of hyponatremia therefore generally is not necessary. Although the hyponatremia normally is without significant impact on the pregnancy or the developing fetus, the physician should be vigilant and monitor patients carefully to detect and treat the hyponatremia when it becomes more severe.

We present a case of a pregnant woman with a history of chronic hyponatremia prior to pregnancy. She was found to have a mutation of the collecting duct vasopressin receptor that made her susceptible to hyponatremia, which was passed on to the child. The impact on the developing fetus is described in an accompanying teaching case.[1] We review the normal physiology of water handling and sodium metabolism in pregnancy, describe potential adverse consequences, and make recommendations for monitoring and therapy.

CASE REPORT

Clinical History and Initial Laboratory Data

A 31-year-old woman was evaluated at 24 weeks' gestation for chronic hyponatremia. She was first noted to have a low serum sodium concentration at the age of 23 years on a routine laboratory test. A limited evaluation revealed persistent mild hyponatremia (serum sodium, 125-136 mEq/L) in the setting of high urine osmolality (456-837 mOsm/kg) and normal serum thyroid-stimulating hormone, free thyroxine, cortisol, renin, and aldosterone levels. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was diagnosed. At the current evaluation, she did not report any concerns and described a total fluid intake of 1 to 1.5 L/d. Her medical history was notable for migraine headaches and hypertension diagnosed at age 23 years, with normal neurohormonal workup findings and renal Doppler ultrasound. Her family history was significant for hypertension in both parents, but no electrolyte abnormalities. Medications included labetalol and a multivitamin. She reported no use of nonsteroidal anti-inflammatory agents or herbal medications. On examination, she was afebrile with blood pressure of 124/76 mm Hg and heart rate of 68 beats/min. Findings from the rest of the examination were normal for her gestational age. Table 1 lists the initial laboratory results.

Additional Investigations

A random serum arginine vasopressin (AVP) concentration was 1.4 pg/mL (concurrent serum sodium, 130 mEq/L). Given the potential risk of inheritance of a mutation by her child, evaluation for nephrogenic syndrome of inappropriate antidiuresis (NSIAD) was performed. Sequencing of the gene encoding AVP receptor 2 (AVPR2; also referred to as V2R) revealed a hemizygous cytosine to thymine substitution at nucleotide 770 of the complementary DNA, resulting in a predicted arginine to cysteine change at amino acid 137. This mutation previously has been reported to result in constitutive activation of AVPR2 and consequent hyponatremia.[2,3]

Diagnosis

NSIAD due to a mutation causing constitutive activation of AVPR2 in pregnancy.

Clinical Follow-up

Early in pregnancy, the patient was encouraged to drink water by her health care providers, and her serum sodium concentration decreased. Serum sodium levels then improved with a 1-L/d fluid restriction and ranged from 125 to 135 mEq/L during her pregnancy. The serum sodium concentration trend before, during, and after pregnancy is shown in Fig 1. Serial obstetric ultrasounds revealed an adequate amniotic fluid index despite the fluid

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Table 1. Initial Laboratory Results

Parameter	Value
Serum sodium (mEq/L)	132
Serum potassium (mEq/L)	3.9
SUN (mg/dL)	8
Scr (mg/dL)	0.7
eGFR (mL/min/1.73 m^2)[a]	129
Serum osmolality (mOsm/kg)	273
Urine osmolality (mOsm/kg)	732
Urine sodium (mEq/L)	174
FE_{Na} (%)	1

Note: Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; SUN, in mg/dL to mmol/L, ×0.357.

Abbreviations: eGFR, estimated glomerular filtration rate; FE_{Na}, fractional excretion of sodium; Scr, serum creatinine; SUN, serum urea nitrogen.

[a]eGFR calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.

restriction. She had no other complications and underwent elective caesarian delivery at term for breech presentation.

DISCUSSION

This case offers the opportunity to review normal sodium and water handling in pregnancy and its clinical implications. It features one of the rarer causes of chronic hyponatremia that should be considered in the differential diagnosis of euvolemic hypotonic hyponatremia in a young woman. In pregnancy, hyponatremia has implications for the developing fetus, and in this case, it becomes particularly relevant when the mother is carrying a male infant.[1]

In healthy nonpregnant individuals, AVP maintains serum osmolality within a tight range of 280 to 290 mOsm/kg. Any increase in serum osmolality is sensed by osmoreceptor cells in the anterior hypothalamus, which direct the signal for AVP release. AVP then acts by AVPR2 on the basolateral membrane of the collecting ducts, leading to upregulation of aquaporin 2 channels on the apical membrane and an increase in water reabsorption. An increase in osmolality also stimulates the thirst center in the hypothalamus, prompting the person to increase water intake. This system is so exact that even a 1% variation in serum osmolality leads to stimulation or suppression of AVP release.[4] In addition to the osmotic stimulus, a nonosmotic stimulus of volume depletion also may result in AVP release. This is a less refined system, requiring at least a 10% reduction in volume or blood pressure before stimulating AVP release.[5]

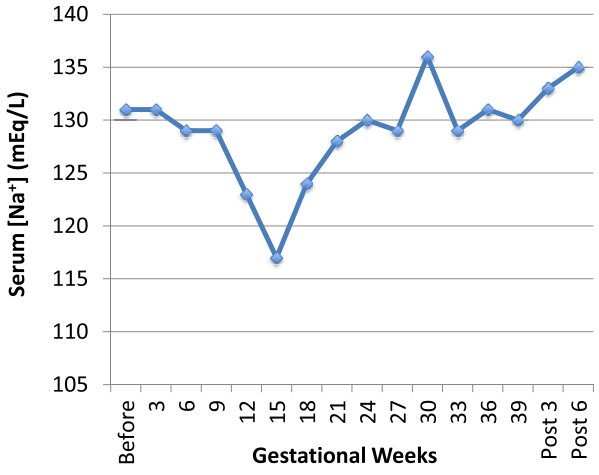

Figure 1. Serum sodium level trend before, during, and after pregnancy. The patient had baseline hyponatremia with sodium levels that decreased early in pregnancy. When fluid restriction was initiated, levels increased to close to normal. Postpartum, they returned to baseline with easing of fluid restriction.

Normal pregnancy results in changes in serum osmolality and serum electrolyte concentrations. Serum osmolality and serum sodium concentration decrease by 10 mOsm/kg and 5 mEq/L, respectively.[6,7] Serum osmolality declines early in pregnancy and reaches a nadir at around 8 to 10 weeks of gestation that then is maintained until the end of pregnancy.[7] Multiple pathways have been postulated to explain this.[8,9] Normal pregnancy "resets" the osmotic set point for AVP release and stimulation of thirst.[6,10] Another widely quoted mechanism is the relative arterial underfilling in pregnancy. Pregnancy is associated with systemic vasodilation attributable to an increase in levels of hormones such as estrogen and relaxin. The systemic vasodilation is countered partially by an increase in cardiac output and neurohormonal activation of the renin-angiotensin and sympathetic systems.[11] Despite compensatory mechanisms, systemic arterial blood pressure decreases and leads to nonosmotic stimulation for AVP release and thirst stimulation.

Metabolism of AVP is significantly altered in pregnancy by the production of vasopressinase by the placental trophoblasts. Vasopressinase, an aminopeptidase, is responsible for degradation of AVP. In normal pregnancy, increased synthesis and secretion of AVP offset the increased vasopressinase activity. However,

Box 1. Factors Leading to Decreased Serum Sodium Levels During Pregnancy and Labor

Related to increased AVP secretion
- Systemic vasodilation and arterial underfilling
- Reset of osmotic set point for AVP release
- Nausea, vomiting (eg, hyperemesis gravidarum)
- Pain

Independent of AVP secretion
- Oxytocin administration
- Polydipsia
- Administration of hypotonic intravenous fluids

Abbreviation: AVP, arginine vasopressin.