Dilutional hyponatremia in pre-eclampsia

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OBJECTIVE: The objective of this report is to describe a defect in water metabolism, characterized by hyponatremia, in patients with pre-eclampsia-induced nephrotic syndrome

STUDY DESIGN: This was an observational study of 3 women.

RESULTS: Hyponatremia was observed in 3 women with pre-eclampsia characterized by various extrarenal manifestations, as well as by nephrotic syndrome with normal or nearly normal renal function. Restriction in water intake partially corrected hyponatremia before delivery in each case, and no complications were observed in the neonates. The mechanism of impaired excretion of water in these patients is proposed to involve persistent and inappropriate production of vasopressin through stimulation of the nonosmotic mechanism for vasopressin secretion in response to a reduction in effective plasma volume.

CONCLUSIONS: These results indicate for the first time that women with pre-eclampsia are, at least when nephrotic, at risk for development of dilutional hyponatremia, which can cause neurologic complications that simulate those of eclampsia. (Am J Obstet Gynecol 1998;179:1312-6.)

Key words: Hyponatremia, pre-eclampsia

Pre-eclampsia is not uncommon and affects approximately 5% of all pregnancies in developed countries. Although generalized edema from retention of sodium is a characteristic feature of this syndrome, hyponatremia from retention of water is not recognized as a complication of either normal pregnancy or pre-eclampsia. A review of the literature disclosed only a single case report of hyponatremia in pregnancy that was associated with pre-eclampsia.[1] This report describes 3 patients with dilutional hyponatremia. Each patient had pre-eclampsia associated with pre-eclampsia–induced nephrotic syndrome, as well as external manifestations of pre-eclampsia. The clinical features exhibited in this small series are described to call attention to the potential risk for hyponatremia in pre-eclampsia, at least when associated with the nephrotic syndrome.

Clinical description of cases

Case 1. A 35-year-old primigravid woman was admitted to the hospital in the 29th week of gestation for pre-eclampsia. The initial antepartum course was characterized by normal blood pressure and absence of proteinuria. At 27 weeks' gestation the patient had headache and epigastric pain. The blood pressure was 140/90 mm Hg and laboratory values included the following: proteinuria (2+), elevated aspartate aminotransferase level (98 U/L) and alanine aminotransferase level (97 U/L), and platelet count 160×10^3 cells/mL. The prothrombin and partial thromboplastin times were normal. She refused hospitalization and had a 15-lb weight gain and dependent edema in the interval before hospital admission. Her medical history was significant for petit mal seizures since she was 16 years old. At onset of pregnancy carbamazepine (Tegretol) was replaced with phenobarbital for seizure control.

At admission to the hospital the patient's blood pressure was 148/88 mm Hg and generalized edema was present. Laboratory values included the following: blood urea nitrogen, 12 mg/dL; serum creatinine, 0.8 mg/dL; uric acid, 4.4 mg/dL; serum sodium, 130 mEq/L; hematocrit, 36%, serum albumin, 2.7 g/dL, urinary protein, 2.9 g/d, aspartate aminotransferase, 72 U/L; alanine aminotransferase, 91 U/L; platelet count 225×10^3 cells/mL; fibrinogen, 580 mg/dL; and fibrin split products 10 to 40 μg/mL. Treatment consisted of bed rest, fetal monitoring, and hydralazine (Apresoline 200 to 400 mg/d) for blood pressure control. On the 30th hospital day hyponatremia (121 mEq/L) was noted, in association with moderate renal insufficiency and worsening of proteinuria and hypoalbuminemia. Pertinent clinical features and laboratory values are shown in Table I. After restriction of oral fluid intake the serum sodium level rose to 134 mEq/L within 6 days and remained at or above that level until delivery, although renal insufficiency (maximum serum creatinine 1.4 mg/dL) and nephrotic syndrome persisted. The patient's hospital course was characterized by moderate hypertension (160/95 mm Hg), persistently elevated liver enzymes, and persistence of fibrin split products but with normal bilirubin, platelet count, and hematocrit values. There

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Table I. Clinical features at onset of hyponatremia

	Case 1	*Case 2*	*Case 3*
Hospital day	30	Admission	14
Blood pressure (mm Hg)	170/100	120/90	140/90
Edema	Marked	Marked	Marked
Blood urea nitrogen (mg/dL)	21	13	23
Creatinine (mg/dL)	1.0	0.7	0.9
Serum sodium (mEq/L)	121	117	129
Urinary sodium (mEq/L)	<10	16	<1
Serum osmolality (mOsm/kg)	258	236	264
Urinary osmolality (mOsm/kg)	628	372	675
Serum albumin (g/dL)	2.2	2.5	2.3
Urinary protein (g/d)	7.0	3.2	4.0

were no clinical features of heart failure and the thyroxine level was 12.6 μg/dL (normally 5-10 μg/dL). A cesarean delivery was performed in the seventh hospital week because of fetal distress and a healthy infant was delivered (Apgar scores of 5 at 1 minute and 8 at 5 minutes). When the patient was discharged 1 week after delivery, blood pressure was 160/100 mm Hg and the laboratory studies showed the following: blood urea nitrogen, 6 mg/dL; serum creatinine, 0.8 mg/dL; serum sodium, 141 mEq/L in absence of fluid restriction; serum albumin, 2.5 g/dL; and urinary protein excretion, 2.3 g/d.

On examination 6 weeks and 15 weeks after delivery, the patient's blood pressure was normal, proteinuria could not be detected by dipstick, and the serum creatinine and sodium levels were 0.9 mg/dL and 142 mEq/L, respectively. A subsequent pregnancy 3 years later was uneventful and resulted in a spontaneous vaginal delivery of a 3440-g infant with an Apgar score of 9 at both 1 and 5 minutes. The patient remains well 8 years after delivery.

Case 2. A 41-year-old primigravid woman was admitted to the hospital in the 37th week of gestation with a presumptive diagnosis of pre-eclampsia and hyponatremia. There was no evidence of hypertension or proteinuria during pregnancy until 4 days before admission, when a blood pressure of 120/90 mm Hg and proteinuria (1+) were observed. A normal blood pressure and absence of proteinuria were documented 2 years before conception. One year before conception the patient had sustained head injury without loss of consciousness in an automobile accident. On admission she had moderate generalized edema and postural symptoms of light-headedness associated with significant changes in blood pressure and pulse rate; blood pressure was 130/90 mm Hg while the patient was recumbent. Results of laboratory studies included the following: blood urea nitrogen, 13 mg/dL; serum creatinine, 0.7 mg/dL; serum sodium, 117 mEq/L; uric acid, 2.1 mg/dL; normal liver function test results; hematocrit, 33%; platelet count, 111×10^3 cells/mL; fibrinogen, 336 mg/dL; fibrin split products <10 μg/mL, serum albumin, 2.5 g/dL; and urinary protein, 3.2 g/d. The thyroxine level was 9 μg/dL. Relevant clinical features and laboratory values are shown in Table I. Mild hypertension persisted at 130/80 to 140/96 mm Hg.

Management included bed rest, fetal monitoring, and restriction of oral fluids. The serum sodium level rose to a level of 132 mEq/L by hospital day 4. On hospital day 5, results of the fetal nonstress test were nonreassuring and biophysical profile testing showed oligohydramnios. The patient was given intracervical prostaglandin gel and several hours later went into labor and was delivered of a healthy 2460-g infant with an Apgar score of 9 at both 1 and 5 minutes. Fluid restriction was continued for 2 to 3 days after delivery until urinary osmolality fell to a level below that of plasma. One week post partum the blood pressure was <140/90 mm Hg and serum sodium was 140 mEq/L in the absence of fluid restriction. Five weeks after delivery the blood pressure was normal (<140/90 mm Hg) and protein excretion was 80 mg/d.

Because of the history of head trauma 1 year before conception, a water-loading test was performed at 10 postpartum weeks. The basal serum osmolality was 288 mOsm/kg (serum sodium 140 mEq/L) with ad lib fluid intake. Ingestion of the water load (1500 mL) resulted in a prompt fall in serum osmolality to 274 mOsm/kg. In contrast, the urine osmolality remained abnormally elevated at 174 mOsm/L (normal <100 mOsm/L). These findings indicate an impaired dilutional capacity as a result of persistent secretion of vasopressin.

Three years after the index pregnancy this patient had a second pregnancy, which was uncomplicated and resulted in a successful vaginal delivery at term. Serum sodium levels and blood pressure remained normal throughout gestation, including during labor and delivery, with unrestricted fluid intake. Results of a water-loading test (1500 mL water) at 10 postpartum weeks were abnormal as before; the minimum urine osmolality achieved between 30 and 90 minutes was 170 mOsm/kg.

Case 3. A 35-year-old primigravid woman with a twin pregnancy was admitted to the hospital at 33 weeks' gestation because of pre-eclampsia. There was no evidence

of hypertension or proteinuria during early pregnancy. At 31 weeks' gestation proteinuria (2+) was noted, and 1 week later protein excretion was 792 mg/d and moderate edema was present. The serum creatinine level was 0.7 mg/dL and the uric acid level was 7.2 mg/dL. The history was significant for the diagnosis of hypothyroidism made 5 years before conception and the incidental finding of a pituitary cyst on magnetic resonance imaging 1 year earlier. The patient was managed with levothyroxine (Synthroid, 225 μg/d during pregnancy) and was judged to be euthyroid on the basis of thyroid-stimulating hormone levels. On admission the patient's blood pressure was 140/90 mm Hg and results of relevant laboratory studies included the following: blood urea nitrogen, 23 mg/dL; serum creatinine, 0.6 mg/dL; serum sodium 132 mEq/L; hematocrit, 33%; platelet count, 120×10^3 cells/mL; normal prothrombin and partial thromboplastin times; fibrinogen, 531 mg/dL, fibrin split products 10 to 40 μg/mL; normal results of liver function tests; serum albumin, 2.3 g/dL; and urinary protein, 4 g/d. Other values included 8.2 μg/dL thyroxine and a morning cortisol level of 18 μg/dL.

Management included bed rest and fetal monitoring while blood pressure ranged between 122/70 and 159/94 mm Hg. Renal function was moderately reduced (serum creatinine 1.1 mg/dL). On the 15th hospital day hyponatremia (129 mEq/L) was observed and oral fluid intake restriction was instituted, resulting in a rise to 136 mEq/L within 4 days. Relevant clinical features and laboratory values are shown in Table I. The onset of labor was induced with oxytocin and limited fluid administration on the 17th hospital day, and healthy twin infants weighing 2650 and 2265 g were delivered. Apgar scores for both twins were 9 and 8 at 1 and 5 minutes, respectively. Four weeks after delivery the patient's blood pressure was 115/70 mm Hg and urinary protein excretion was normal by dipstick test. The patient remains well 2 years after the index pregnancy. Because of the presence of a pituitary cyst, a water-loading test (1500 mL) was performed 10 weeks after delivery. The reduction in serum osmolality to 273 mOsm/kg was associated with a urinary osmolality of 80 mOsm/kg. These results indicate a normal capacity for urine dilution.

Comment

All 3 patients had pre-eclampsia on the basis of onset after week 20 of gestation of hypertension and proteinuria that resolved completely during the puerperium. During a follow-up of 3 to 8 years all patients maintained normal blood pressure and absence of proteinuria. In addition, all patients exhibited various extrarenal features of pre-eclampsia including elevation in liver enzymes, thrombocytopenia, and fibrin split products. During the course of hospitalization 2 patients had moderate reduction in renal function, reflected by elevation of serum creatinine to >0.8 mg/dL, and all 3 exhibited nephrotic syndrome. Although protein excretion usually increases to levels of 0.5 to 2.0 g in pre-eclampsia, previous studies demonstrated proteinuria in the nephrotic range in some patients and suggested that pre-eclampsia may be the most common cause of nephrotic syndrome that occurs de novo during pregnancy.[2] The prompt and complete postpartum resolution of proteinuria in these 3 patients indicates that it was caused by pre-eclampsia.

In an elegant series of studies Davison et al[3] demonstrated that normal pregnancy is associated with a reduction in the osmotic threshold for the release of vasopressin from 280 to about 272 mOsm/kg water and a fall in serum sodium of approximately 5 mEq/L. The sensitivity for control of vasopressin release around the new osmotic threshold, however, remains similar to control values. In the same studies Davison et al[3] showed that healthy gravid women exhibit a prompt reduction in urine osmolality to 78 ± 52 mOsm/Kg in late pregnancy after an oral load of 1 L water, a value that was not different from the level in the same women when not pregnant.

It is clear that vasopressin release was excessively high in this series of patients because urinary osmolality exceeded plasma osmolality levels at the time when plasma osmolality was at least 10 mOsm/kg lower than the usual normal osmotic threshold expected in pregnancy, as shown in Table I. The actual serum sodium levels attained in these patients probably reflected variations in fluid intake and the time delay before restriction of fluid intake was initiated, rather than individual differences in the abnormal osmotic set-point. For example, patient 3 was carefully monitored with measurements of serum sodium because the same group of obstetricians had previously managed patient 2 and were therefore aware of the potential complication of hyponatremia in patients with pre-eclampsia–induced nephrotic syndrome. Because urinary osmolality was >600 mOsm/k when serum sodium fell to 129 mEq/L, a further decrease in sodium concentration would have been expected if fluid intake had not been promptly restricted. The clearance of water was actually negative in the present series because the ratio of urinary to plasma osmolality was >1.0 in all patients.

This observational study was not designed to examine the mechanism of hyponatremia in these pregnant patients. However, insights into the probable cause of hyponatremia can be derived from the established mechanism for free water clearance in healthy individuals and from insights derived from nonpregnant patients with the nephrotic syndrome and from patients with pre-eclampsia. The clearance of free water (C_{HOH}) is described by the following equation: $C_{HOH} = V - (V \times {}^{Uosm}/_{Posm})$, where *V* represents the volume, *Uosm* represents urinary osmolality, and *Posm* represents plasma os-

molality. A positive value is achieved only when the ratio of urinary to plasma osmolality is <1 and increases as a function of the decrease in this ratio and the rate of formation of solute-free water in the water-impermeable diluting segment in the kidney from solute reabsorption. A reduction in free water clearance therefore occurs when the quantity of sodium delivered to the diluting segment is reduced or the mechanism for sodium absorption in the diluting segment is impaired or when levels of vasopressin are sufficiently high to cause reabsorption of water in the collecting duct system and thus a reduction in diluting capacity.

In healthy euvolemic adults, whether pregnant or not, the ingestion of at least 1 L water results in a rapid fall in urinary osmolality to <100 mOsm/kg (a normal dilution capacity) and free water clearance of approximately +10 mL/min.[3, 4] In contrast, patients with the nephrotic syndrome, as well as patients with congestive heart failure, decompensated liver disease, and myxedema, exhibit a decrease in both the diluting capacity and rate of free water clearance.[5-8]

There is substantial evidence that the reduced free water clearance in nephrotic syndrome is caused by a reduction in the quantity of sodium delivered to the diluting segment, caused by increased absorption of sodium in the proximal tubule. This hypothesis is supported by the demonstration that free water clearance is increased in patients with edema but not in healthy subjects when mannitol, which reduces sodium reabsorption in the proximal tubule, is infused.[6, 7] Although plasma volume is not measurably decreased in supine patients with nephrotic syndrome (see Smith and Hayslett[10] for review), it is clearly reduced in the upright position.[11] It has therefore been proposed that a fall in effective, or circulating, plasma volume acts to stimulate proximal sodium absorption by the kidney, thus decreasing the amount of sodium delivered to the diluting segment.[12] Furthermore, the level of atrial natriuretic peptide in venous blood, a measure of right atrial fullness, is significantly reduced in nephrotic syndrome compared with values in healthy subjects.[13]

The impaired ability to excrete free water in nephrotic syndrome is also related to a partial reduction in maximal urinary dilution,[5] reflected by a minimal urinary osmolality of 150 to 200 mOsm/kg, apparently caused by nonosmotic release of vasopressin triggered, perhaps, by a decrease in effective plasma volume.[14] Usberti et al,[15] for example, showed that, in contrast to healthy subjects, vasopressin levels were not decreased by a water load in patients with nephrotic syndrome and serum albumin levels <2.0 mg/dL. The continued release of vasopressin would be expected to stimulate free water absorption in the collecting duct system. A similar condition might be expected in pre-eclampsia because a reduction in plasma volume is a well-documented complication.[16]

Plasma vasopressin levels were not measured in these patients because high vasopressinase levels, characteristic of pregnancy, would have degraded the hormone and invalidated measurements in stored plasma.[17] It seems certain, however, that vasopressin levels were elevated because this is the only means of increasing the ratio of urinary osmolality to plasma osmolality to >1. Because plasma osmolality was ≥10 mOsm/kg lower than the normal set-point for release of vasopressin in pregnancy, it seems likely that the nonosmolar mechanism for vasopressin release was activated by a low effective plasma volume induced by the additive effects of nephrotic syndrome and possibly pre-eclampsia. The chronic inability to normally dilute urine in patient 2 was probably an additional factor in the development of dilutional hyponatremia. Because head trauma may result in the inappropriate release of vasopressin,[18, 19] it seems likely that the disorder in water metabolism in this patient was caused by the head trauma that preceded pregnancy. It is important to note, however, that the persistent inappropriate release of vasopressin alone in this patient was insufficient to cause hyponatremia in the absence of pre-eclampsia, because hyponatremia was not detectable in the nonpregnant state or during a subsequent pregnancy.

It is well known that reduction in serum osmolality may cause disruption of cellular osmoregulatory mechanisms and cerebral edema, as recently reviewed by McManus et al.[20] The occurrence of cerebral dysfunction and severity of complications correlate with the absolute reduction in serum osmolality and its rate of fall. Because water concentration equilibrates across the placenta, it was assumed that each of the fetuses in this series was also hyponatremic. The treatment instituted in these cases was conservative, with the aim of achieving a serum concentration of sodium of ≥130 mEq/L by delivery. Fortunately there was no evidence of fetal neurologic injury at birth or subsequently.

Although the observations in this small series of patients do not indicate the incidence of this phenomenon in pre-eclampsia, they serve to highlight an unrecognized complication, at least in the subset of patients with the nephrotic syndrome. The neurologic manifestations of hyponatremia are similar to those seen in eclampsia but require markedly different treatment strategies.

REFERENCES

1. Sutton RA, Schonholzer K, Kassen BO. Transient syndrome of inappropriate antidiuretic hormone secretion during pregnancy. Am J Kidney Dis 1993;21:444-5.
2. Fisher KA, Ahuja S, Luger A, Spargo BH, Lindheimer MD. Nephrotic proteinuria with pre-eclampsia. Am J Obstet Gynecol 1977;129:643-6.
3. Davison JM, Gilmore EA, Durr J, Robertson GL, Lindheimer MD. Altered osmotic thresholds for vasopressin secretion and thirst in human pregnancy. Am J Physiol 1984;246:105-9.
4. Schoen EJ. Minimum urine total solute concentration in re-

sponse to water loading in normal men. J Appl Physiol 1957;10:267-70.
5. Gut A, Adefuin PY, Siegel NJ, Hayslett JP. A study of the renal handling of water in lipoid nephrosis. Pediatr Res 1976;10:197-201.
6. Schedl HP, Bartter F. An explanation for an experimental correction of the abnormal water diuresis in cirrhosis. J Clin Invest 1960;39:248-61.
7. Bell NH, Schedl HP, Bartter FC. An explanation for abnormal water retention and hypoosmolality in congestive heart failure. Am J Med 1964;36:351-60.
8. Skousky WR, Kibuchi TA. The role of vasopressin in the impaired water excretion of myxedema. Am J Med 1978;64: 613-20.
9. Kleeman, CR, Adams DA, Maxwell MH. An evaluation of maximal water diuresis in chronic renal disease 1. Normal solute intake. J Lab Clin Med 1961;58:169-84.
10. Smith D, Hayslett JP. Reversible renal failure in the nephrotic syndrome. Am J Kidney Dis 1992;9:201-13.
11. Eisenberg S. Postural changes in plasma volume in hypoalbuminemia. Arch Intern Med 1963;112:544-9.
12. Peters JP. The role of sodium in the production of sodium. N Engl J Med 1948;239:353-62.
13. Peterson C, Madsen B, Pertman A, Chan AY, Myers BD. Atrial natriuretic peptide and the renal response to hypervolemia in nephrotic humans. Kidney Int 1988;34:825-31.
14. Baylis PH. Osmoregulation and control of vasopressin secretion in healthy humans. Am J Physiol 1987;253:671-8.
15. Usberti M, Federico S, Meccariello S, Cianciaruso B, Balletta M, Pecorado C, et al. Role of plasma vasopressin in the impairment of water excretion in nephrotic syndrome. Kidney Int 1984;25:422-9.
16. Gallery ED, Hunyor SN, György AZ. Plasma volume contraction: a significant factor in both pregnancy-associated hypertension (pre-eclampsia) and chronic hypertension in pregnancy. Q J Med 1979;48:593-602.
17. Davison JM, Sheills EA, Barron WM, Robsinson AG, Lindheimer MP. Changes in the metabolic clearance of vasopressin and in plasma vasopressin throughout human pregnancy. J Clin Invest 1989;83:1313-8.
18. Born JD, Hans P, Smitz S, Legros JJ, Kay S. Syndrome of inappropriate secretion of antidiuretic hormone after severe head injury. Surg Neurol 1985;23:383-7.
19. Doczi T, Tarjanyi J, Husyka E, Kiss J. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after head injury. Neurosurgery 1982;10:658-68.
20. McManus ML, Churchwell KB, Strange KE. Regulation of cell volume in health and disease. N Engl J Med 1995;333:1260-6.