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CASE REPORT

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The role of hyponatremia in preeclampsia

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Abstract

Preeclampsia associated hyponatraemia is a quite rare condition that cannot be separated from preeclampsia with severe features completely. This condition may be life-threatening for mothers and fetuses and is needed a multidisciplinary management. A 31-year-old primigravida was referred to our perinatology clinic at 28 weeks 4 days due to preeclampsia. She had nephrotic proteinuria and developed hypervolemic, hypoosmolar, chronic, severe hyponatremia. The pregnant was delivered at 29 weeks of gestation because of severe preeclampsia. The baby died in 48 hours postpartum and maternal hyponatremia improved spontaneously within 72 hours. Studies major on vasopressin about hyponatremia-complicated preeclampsia that its pathogenesis and management is still unclear. Studies that note the importance of vasopressin in the pathogenesis of preeclampsia support the theories and highlight the association of vasopressin and hyponatremia. It is known that the definite treatment is delivery. Maternal outcomes are good but neonatal outcomes are variable.

Keywords: Hyponatremia, preeclampsia, pregnancy, nephrotic, vasopressin

Introduction

Preeclampsia is defined as a pregnancy-specific syndrome that can affect virtually every organ system complicates 2–8% of pregnancies [1,2]. Preeclampsia associated hyponatraemia is a quite rare condition that cannot be separated from preeclampsia with severe features completely and may be life-threatening for mothers and fetuses and is needed a multidisciplinary management [3-6]. Here we present a case of severe hyponatremia in a patient with preeclampsia. We also reviewed the literature to find out all reported cases about preeclampsia that were complicated by hyponatremia.

Case Report

A 31 year old primigravida was referred to us at 28 weeks 4 days with preeclampsia and oligohydramnios. She had no significant medical history and the pregnancy to date had been uneventful. Her blood pressure was under control by 750 mg/day methyldopa. Physical examination showed that mental status was normal, no fever, heart rate was 77/minute and blood pressure 140/79 mmHg. Heart sounds were regular and no murmur was heard. Lung examination was normal but bilateral pedal edema was present. Fetal growth was consistent with the gestational week and there was borderline/low normal amniotic fluid volume. Middle cerebral artery, umbilical artery and ductus venosus doppler were normal. Fetal cardiotocograph had neither fetal distress nor premature contractions.

Laboratory tests showed the following values: hemoglobin, 12.3 g/dl (reference range: 12-16.6 g/dl); platelets, 193 $x10^3$/uL (reference range: 150-450 $x10^3$/uL); prothrombin time, 9.2 second (reference range: 9.4-12.5 sec); INR, 0.86 (reference range: 082-1.17); activated partial thromboplastin time, 28.3 sec (reference range: 25-38 sec); fibrinogen, 277 mg/dl (reference range: 180-400 mg/dl); serum sodium, 132 mEq/L (baseline, 135 mEq/L at 28 weeks of gestation); potassium, 4.1 mEq/L (reference range: 3.5-5.1 mEq/L); serum urea nitrogen, 28 mg/dL (reference range: 0-50 mg/dL); serum creatinine, 0.6 mg/dL (reference range, 0.7-1.4 mg/dL); and estimated glomerular filtration rate, 128 mL/min/1.73 m2 (2.1 mL/s/1.73 m2); serum AST, 37 U/L (reference range <35 U/L); serum ALT, 51 U/L (reference range <35 U/L); serum LDH, 299 U/L (reference range <248 U/L); serum total protein, 5.7 g/dl (reference range 6.4-8.3 g/dl); serum albumin, 2.88 g/dl (reference range 3.3-5.2 g/dl) and serum uric acid level was normal. Spot urine analysis had 500 mg/dl proteinuria. 24-hour urine protein analysis was 6400 mg. She was administered 12 mg betamethasone x 2 doses to accelerate fetal lung maturity.

At 29 weeks, her blood pressure increased to 156/99 mmHg and 162/100mmHg. Laboratory tests showed the following values: hemoglobin, 11.8 g/dl (reference range

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12-16.6 g/dl); platelets, 179 x10^3/uL (reference range 150-450 x10^3/uL); prothrombin time, 9.2 sec (reference range 9.4-12.5 sec); INR, 0.86 (reference range 082-1.17); activated partial thromboplastin time, 26.2 sec (reference range 25-38 sec); fibrinogen, 273 mg/dl (reference range 180-400 mg/dl); serum sodium, 120 mEq/L (baseline, 135 mEq/L at 28 weeks of gestation); potassium, 4.2 mEq/L (reference range, 3.5-5.1 mEq/L); serum urea nitrogen, 25 mg/dL (reference range, 0-50 mg/dL]); serum creatinine, 0.6 mg/dL (reference range, 0.7-1.4 mg/dL); and estimated glomerular filtration rate, 128 mL/min/1.73 m2 (2.1 mL/s/1.73 m2); serum AST, 38 U/L (reference range <35 U/L); serum ALT, 42 U/L (reference range <35 U/L); serum LDH, 290 U/L (reference range <248 U/L); serum total protein, 5.1 g/dl (reference range 6.4-8.3 g/dl); serum albumin, 2.6 g/dl (reference range 3.3-5.2 g/dl) and serum uric acid level was normal. Free T3, 2.73 pg/ml (reference range 2.5-3.9 pg/ml); free T4, 0.98 ng/dl (reference range 0.61-1.12 ng/dl); TSH, 5.2 mIU/ml (reference range 0.3-3 mIU/ml[1]); cortisol, 17.4 mcg/dl (reference range 6.7-22.6 mcg/dl); serum total calcium 7.7 mg/dl; corrected serum calcium 8.9 mg/dl[2] (reference range 8.4-10.2 mg/dl); spot urine analysis had 20 mEq/L sodium; urine osmolality was 189 mOsm/kg, serum osmolality was 255 mOsm/kg; 24-hour urine protein analysis was 7254 mg. She was administered with fluid restriction, dietary including 2g/day salt and thyroxin 25 mcg/day. Electrocardiogram was normal. Her treatment was continued with increased dose of methyldopa to 1500mg/day.

Between 29 and 30 weeks, her serum sodium levels were fluctuating from 121 to 128 mEq/L. At the week of 29.4, her blood pressure escalated to 163/110 and 165/110. Additionally her platelets decreased to 80 x10^3/uL and she had headache with visual symptoms. She was administered magnesium sulfate for seizure prophylaxis [1] and then delivered by caesarean section of deteriorating hyponatraemia and worsening symptoms of preeclampsia. A female infant weighing 1.21 kg was delivered. First and fifth minute Apgar scores were four and six. Her blood gas analysis results: pH: 7.24, pCO2: 44, HCO3: 18, BE: -7.5, pO2: 38. The infant had hyponatremia and respiratory distress syndrome (RDS). Her sodium was 120 mEq/L and the newborn was administered by surfactant and sodium. But it was a resistant hyponatremia that decreased to 105 mEq/L despite the treatment. So the newborn died 2 days postpartum because of RDS and hyponatremia. On the other hand within 72 hours after delivery, maternal serum sodium increased to 132 mEq/L. She was discharged 5 days postpartum (Table 1). Her blood pressure, urine analysis and platelets were normal at six weeks postpartum and all antihypertensive drugs were discontinued.

Table 1. The results of routine and additional biochemical investigations

	DAYS									
Laboratory investigation results (normal values at third trimester)	1 Admission	4	5	6	7	8 Delivery	9 post operative	10	11	13 Discharge
Hemoglobin, g/dl (9.5-15)	12.3	11.8	11.7	11.7	13	13	11.9	11.5	11.9	10.4
Platelets, 10^3/uL(150-450)	193	179	123	128	118	80	75	64	110	110
PT, second (9.6-12.9)	9.4	9.4	9.5	9.3	8.9	8.5	8.2			9.1
INR (0.8-1.09)	0.9	0.86	0.86	0,8	0.8	0.79	0.77			0.85
aPTT , second (22-35)	28.3	26.2	27.7	30.4	29	33	28.6			32
Fibrinogen, mg/dl (180-400)	277	273	334	279	298	294	214			387
Fasting glucose, mg/dL	100	92	89	91	87	88	91			92
Sodium,mEq/L (130 – 148)	132	120	128	122	125	123	119	124	132	138
Potassium, mEq/L (3.5-5.1)	4.1	4.2	4.2	4.2	4.6	4.8	4.57	4.5	4.3	4.2
Total Calcium, mg/dl (8.2-9.7)	8.2	7.7	8.4	8.02	7.5	7.45	7.19	6.92	7.02	7.7
BUN, mg/dL (3-24)	28	25	18	22	26	44	43	37	24	13
Creatinine, mg/dL (0.4-0.9)	0.62	0.66	0.53	0.63	0.6	0.79	0.89	1	0.79	0.71
AST, U/L (4-32)	30	32	28	27	31	31	33	36	47	43
ALT, U/L (2-25)	31	32	28	28	26	29	18	15	44	47
LDH, U/L (82 - 524)	299	290	247	298	323	410	526	556		478
Total protein, g/dl (5.6-6.7)	5.71	5.18	4.64	4.58	4.5	4.44	4.21	4.2		4.69
Albumin, g/dl (2.3-4.2)	2.88	2.65	2.39	2.28	2.07	2.03	2.17	2.3	2.5	2.31
TSH, mIU/ml (0.38-4.04)	3.5									
Cortisol, µg/dL (12-50)	17.44									
Serum Osmolality, mOsm/kg (278 – 280)	255		257							
Urine investigation results										
24 hour urine protein, mg/24 hour (46-185)	6400		7254			9963				
Spot urine sodium, mEq/L	20		33							
Urine Osmolality, mOsm/kg (238-1034)	189		273							

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, aPTT: activated partial thromboplastin time, BUN: serum urea nitrogen, INR: International normalized ratio, LDH: lactate dehydrogenase, PT: prothrombin time, TSH: Thyroid-stimulating hormone

Table 2. Literature review of all reported cases with hyponatremia in preeclampsia

Authors	Age (years)	Risk factors and diseases	Lowest Serum Na (mEq/L)	Uosm/Sosm (mOsm/kg)	Urine Na (mEq/L)	Type of hyponatremia/ Reason	Nephrotic syndrome	AFI/Fetal growth	Indication of induction	Gestation at delivery (weeks)	Mode of delivery	Maternal/ Neonatal outcome
Goodlin (1987)[15]	28	None	119	_	<10	_/_	No	_/_	HELLP syndrome	28	_	Good/Hyponatremia
Sutton (1993)[11]	41	Graves' disease, viral encephalopathy	120	537/249	53	Normovolemic/ SIADH	No	_/_	Preeclampsia at term, severe hyponatremia	37	_	Good/_
Hayslett (1998) case 1[8]	35	Nulliparity, epilepsy, renal failure	121	628/258	<10	Hypervolemic/ Dilutional	Yes	_/_	Fetal distress	33	_	Good/_
Hayslett (1998) case 2[8]	41	Nulliparity, head trauma	117	372/236	16	Hypervolemic/ Dilutional	Yes	Oligohydramnios/ _	Preeclampsia at term, fetal distress	37	_	Good/_
Hayslett (1998) case 3[8]	35	Nulliparity, twins, hypothyroidism, pituitary cyst	129	675/264	<1	Hypervolemic/ Dilutional	Yes	_/_	Severe preeclampsia	35	_	Good/_
Magriples (2001) case 1[7]	30	Twins	120	630/263	_	Hypervolemic/ Dilutional	Yes	_/_	Severe hyponatremia	33	_	Good/Good
Magriples (2001) case 2[7]	30	Nulliparity, twins	120	311/261	_	Hypervolemic/ Dilutional	No	_/_	Preterm labor, severe hyponatremia	30	Vaginal	Good/Good
Burrell (2004)[6]	31	Nulliparity	119	348/256	<20	Hypervolemic	No	Oligohydramnios/ Third percentiles	Severe hyponatremia, severe preeclampsia	33	C/S	Good/Hyponatremia
Ravid(2005)[3]	33	Nulliparity, twins	122	270/257	31 mEq/24h	Normovolemic/ SIADH	No	Normal/Normal	Preeclampsia at term	38	C/S	Good/Good
Ray(2006)[12]	38	Nulliparity	123	279/261	65	Normovolemic/ SIADH	No	Polyhydramnios/ Normal	Preeclampsia at term	37	C/S	Good/Good
Wilson(2007)[13]	32	Nulliparity	116	656/260	62	Normovolemic/ SIADH	Yes	_/_	Severe preeclampsia	34	C/S	Good/Hyponatremia
Linton(2009)[9]	33	Nulliparity	117	495/242	<20	Hypervolemic	No	_/Normal	Preeclampsia at term	37	C/S	Good/Good
Jhaveri(2009)[5]	35	Twins	117	423/245	_	_	No	_/_	_	34	C/S	Good/_
Sandhu(2010)[14]	30	Nulliparity	123	325/266	77	Normovolemic/ SIADH	Yes	Normal/Normal	Severe hyponatremia, severe preeclampsia	35	Vaginal	Good/Hyponatremia
Camara-Lemarroy (2013)[4]	25	Twins	113	490/238	9	Hypervolemic	No	Normal/Normal	Severe preeclampsia, severe hyponatremia	25	C/S	Good/Both hyponatremia, RDS, sepsis, death
Our case	31	Nulliparity, subclinical hypothyroidism	120	189/255-273/257	20-33	Hypervolemic	Yes	Oligohydramnios/ Normal	Severe preeclampsia	29	C/S	Good/Hyponatremia, RDS, sepsis, death

Material and Methods

An extensive literature research was performed by using Medline, Embase and the Cochrane Database to find out all reported cases about preeclampsia that were complicated by hyponatremia. We reached 15 reported cases. Our case is sixteenth according to our knowledge (Table 2). We concluded that our patient had a hypervolemic, hypoosmolar, severe and chronic hyponatremia and nephrotic syndrome. In the published cases, eight pregnancies developed hypervolemic hyponatremia [6-10], five pregnancies had SIADH (Syndrome of Inappropriate Antidiuretic Hormone) with all criterias [3,11-14] six patients were presented with nephrotic syndrome [7,8,13,14] and one case complicated by HELLP syndrome [15].

Our purpose of publishing this case is to review, which risk factors all reported cases about preeclampsia which were complicated by hyponatremia included, when, what kind of indication and how they were delivered and to observe maternal and neonatal outcomes. Additionally we intend to express which situations we have to take notice about these cases' follow up and treatment and to highlight the role of hyponatremia in preeclampsia with pioneering recently published studies.

Discussion

Serum sodium concentration is maintained by a homeostatic mechanism involving antidiuretic hormone (ADH) also known as vasopressin, thirst and renal reabsorption of sodium. ADH is released in response to elevated plasma osmolality, decreased extracellular fluid volume, pain, stress and some drugs [16,17].

Hyponatremia is commonly defined as a serum sodium concentration below 135 meq/L and it is considered severe hyponatraemia when the level is below 120 meq/L. Severe form can cause coma or grand mal seizure even death. Acute and severe hyponatremia necessitates emergency care with rapid restoration of normal osmotic milieu [17].

Hyponatremia can be classified into two groups: hyponatremia due to non-osmotic hypersecretion of ADH (hypovolemic, hypervolemic, euvolemic) and hyponatremia of non-hypervasopressinemic origin [18,19]. Hypovolemic hyponatremia can arise in a variety of settings for example in diarrhea, vomiting or other gastrointestinal fluid losses. Patients with clinical symptoms or signs of volume depletion should be considered to be hypovolemic. Elevations of blood urea nitrogen, creatinine, and uric acid level are helpful laboratory clues to the presence of volume depletion. Measuring the urine sodium excretion is considered (it should be <20 to 30 mmol/L) [19,20].

Euvolemic (normovolemic) hyponatremia which is most often associated with the SIADH also known as Schwartz-Bartter syndrome but can also be seen with primary polydipsia, a low dietary solute intake, renal failure and endocrine disorders such as hypothyroidism and secondary adrenal insufficiency [17,20]. Despite hypoosmolality ADH release is not fully suppressed in SIADH. SIADH remains a diagnosis of exclusion; other causes of hyponatremia must be excluded [17].

Disorders associated with hypervolemic hyponatremia, which is with urine sodium level <10 mEq/L (etc. cardiac failure and liver cirrhosis) all manifest edema formation due to renal sodium and water retention [18].

These groups can also classify by serum osmolality. The three most common causes of hyponatremia with a high or normal serum osmolality are marked hyperglycemia, severe azotemia, and alcohol intoxication. Less common causes of hyponatremia with a high or normal serum osmolality contain infusion or absorption of solutions including sugars that act as effective osmoles, systemic absorption of irrigant solutions including glycine, sorbitol, or mannitol, and pseudohyponatremia due to hyperlipidemia or hyperproteinemia [17-19].

A healthy pregnancy is characterized by increased water retention and resetting of osmotic threshold for thirst [21]. Decreased osmotic thresholds for ADH release has been shown during pregnancy. Pregnant women experience a desire to drink at a lower plasma osmolality. Additionally AVP metabolism is significantly changed in pregnancy. All of these lead to in a decrease in serum sodium concentration and serum osmolality by approximately 5 mEq/L and 10 mOsm/kg, respectively [21-23]. Although mild hyponatremia is part of the normal physiology of pregnancy, other factors may exacerbate this decline in serum sodium levels such as sodium restriction, polydipsia or inappropriate hypotonic intravenous fluid therapy [11,17]. Nausea, vomiting, and pain that are commonly seen in pregnancy and labour can stimuli AVP secretion. Using of the oxytocin, which is structurally similar to AVP, can mimic AVP activity [16,23].

The mechanism of hyponatremia in preeclampsia has been understood poorly. It has been suggested that SIADH and low effective plasma volume that it leads to a non-osmotic release of ADH can cause of development of hyponatremia during preeclampsia [13,14].

In this case, she had a low serum osmolality, which was 255 mOsm/kg. The two most common causes of hyponatremia with a low serum osmolality are effective arterial blood volume depletion and the SIADH secretion, both of which are associated with persistent ADH release [24]. Of course we know that intravascular volume may be reduced in preeclampsia with severe features. There is no evidence of underfilling of the arterial circulation; rather,

the decreased volume appears to be a consequence of vasoconstriction from enhanced responses to vasoactive substances. This issue has not been definitely resolved [2]. Most patients with hyponatremia have a single cause but, in some patients, multiple factors lead to the fall in serum sodium. Symptomatic infection with human immunodeficiency virus (HIV) is an example of this phenomenon, as volume depletion, SIADH, and secondary adrenal insufficiency all may be present. Separately, hyponatremia can be defined as hyperacute, acute, subacute and chronic hyponatremia that the hyponatremia developed over just a few hours, within the previous 24 hours, within the previous 24-48 hours and has been present for more than 48 hours, respectively [16-19]. Hyperacute hyponatremia with a sodium level of 120 mEq/L can lead to a brain herniation but the same sodium level with chronic hyponatremia may not cause any manifestations [17,18]. Firstly we thought that together SIADH and hypothyroidism could contribute to hyponatremia in our patient. Actually, she did not have hypothyroidism that can cause hyponatremia because hyponatremia can develop only in moderate or severe hypothyroidism, particularly in primary hypothyroidism and myxedema. Our case had just subclinical hypothyroidism. A low serum osmolality, an inappropriately elevated urine osmolality (above 100 mosmol/kg and usually above 300 mosmol/kg), an urine sodium concentration usually above 40 meq/L, low blood urea nitrogen and serum uric acid concentration, a relatively normal serum creatinine concentration, normal acid-base and potassium balance, normal adrenal and thyroid function are the findings in SIADH [25]. But she did not have all of the these findings and she had significant bilateral edema thus we can discount SIADH.

Nausea, malaise, dizziness, gait disturbances, forgetfulness and muscle cramps are more common findings in hyponatremia. Headache, confusion, lethargy, obtundation, seizure, coma, respiratory arrest and noncardiogenic pulmonary edema are less common but the severe ones [26]. It is difficult to discriminate that nausea, headache and dyspnea are due to hyponatremia or preeclampsia.

This is the third case, which had oligohydramnios [6,8]. Only one case was reported with polyhydramnios [12]. How can polyhydramnios occur? Fetal sodium rapidly equilibrates with maternal sodium so hyponatremia can quickly develop in fetus. Its results in the short run were fetal tachypnea and seizures. Ultimately fetal jaundice or polyhydramnios may develop due to supression of fetal arginin vasopressin [14]. Seven babies had neonatal hyponatremia [4,6,13-15] and three of them were (both of twins and our case) died at postpartum 48 hours [4]. As we recognized from the Table 2, hyponatremia in preeclampsia is a serious complication that is increasing the ratio of Caesarean section and may be the reason of neonatal morbidity and mortality.

How can we treat hyponatremia in preeclampsia? Fluid restriction, oral salt tablets and intravenous saline may been administered alone or together if patient has SIADH [17].

Furosemide and vasopressin receptor antagonists(VRA) are FDA class C drugs [16]. Placental hypoperfusion and fetal electrolyte abnormalities were reported with furosemide. VRA related adverse events were observed in animal reproduction studies and there is not any studies with human pregnancies. Demeclocycline and lithium are FDA class D drugs and do not have to be used in pregnancy. But we have shown what hyponatremie's definite treatment in preeclampsia by all of 16 cases that was delivery. Close blood pressure, laboratory and fetal well-being monitoring is suggested during pregnancy because it is not clear when disease will develop to severe preeclampsia, HELLP syndrome [15] or be complicated by fetal distress [8].

Treatment of hyponatremia also can be dangerous if there is a quick rise of serum sodium level. Overly rapid correction of severe hyponatremia can lead to a severe and sometimes irreversible neurologic disorder called the osmotic demyelination syndrome (previously called central pontine myelinolysis) [17]. It was a complicated case that including increased extracellular volume due to nephrotic proteinuria and then non-osmolar release of ADH lead by effective arterial volume depletion due to preeclampsia and hypoalbuminemia as some cases that described before [7,8]. One of the other theories of which try to demonstrate hyponatremia in preeclampsia is impaired releasing of vasopressinase due to placental dysfunction [11,27]. Before this, a mechanism had been proposed that related to oxytocin, vasopressin and their products were raised by premature contractions and preterm labor [22]. Furthermore, increased vasopressin levels are in doubt about preeclampsia as other low-renin hypertensive states and copeptin has been reported which is surrogate of vasopressin is an useful biomarker for the prediction of preeclampsia [28]. It highlights the role of hyponatremia in preeclampsia that is severity. Hyponatremia may be a criteria for severe preeclampsia in future but now it is too early and ostentatious to talk about that. More cases and case-control studies are needed.

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