Case report

Hyponatraemia compounding pre-eclamptic toxaemia in a patient with type 1 diabetes

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SUMMARY

We report a case of profound, symptomatic hyponatraemia in association with pre-eclamptic toxaemia (PET) in a 38-year-old nulliparous woman with type 1 diabetes mellitus. This patient developed hypertension and proteinuria at 31+6 weeks' gestation and was admitted for management of pre-eclampsia. Severe headache, visual disturbance and nausea were associated with a hyponatraemia of 115 mmol/L followed by ketoacidosis. This was reversed through fluid restriction, supplementation with 1.8%–3.0% hypertonic saline and a volume-reduced variable-rate insulin infusion. Clinical stability was achieved and she was subsequently worked up for an induction of labour for worsening pre-eclampsia. Hyponatraemia in the context of PET has been previously reported as rare. However, it has complications that may significantly compound the sequelae of severe PET. We propose that specific and focused monitoring of serum sodium levels should become common practice in the management of women with this condition to allow for timely, measured correction of abnormalities.

BACKGROUND

Pre-eclamptic toxaemia (PET) is one of the leading causes of direct maternal morbidity and mortality worldwide.[1] It is a common antenatal condition that occurs after 20 weeks' gestation and is categorised by new-onset, persistent hypertension (systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg) with one or more of concurrent proteinuria (≥0.3 g/24 hours), evidence of systemic involvement or fetal growth restriction (FGR), a manifestation of severe uteroplacental insufficiency.[2] The pathophysiology is not yet fully understood but is characterised by insufficient trophoblastic invasion and a complex maternal immune response associated with the release of inflammatory and anti-angiogenic metabolites resulting in endothelial dysfunction, maternal vasoconstriction and increased capillary permeability.[3] In the majority of cases, the mainstay of treatment is blood pressure control until the fetus is mature at which point delivery is recommended. However, in a small group of patients, escalation of the disease leads to a multitude of complications such as kidney injury, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and FGR as well as dramatic fluid shifts causing pulmonary or cerebral oedema necessitating maternal stabilisation prior to urgent delivery.

We report a case of severe symptomatic hyponatraemia in a patient with type 1 diabetes mellitus and atypical pre-eclampsia to highlight the importance of early recognition, discuss potential pathophysiology and propose management strategies.

CASE PRESENTATION

A 38-year-old para 0+1 presented with headache and proteinuria at 31+6 weeks' gestation.

She had a history of type 1 diabetes mellitus that was managed with a basal-bolus insulin regime. On booking, at 7 weeks' gestation, her haemoglobin A1c (HbA1c) was 63 mmol/mol. Her previous pregnancy resulted in miscarriage and had been managed surgically at 12 weeks' gestation. She had had a cone biopsy at the age of 24, which was followed up with normal smears. During her pregnancy she was seen fortnightly in a joint-care obstetric/diabetes clinic as well as a consultant-led prematurity clinic for cervical length surveillance. She was taking regular progesterone at a dose of 400 mg per day per vaginum for prevention of preterm labour. She developed mild diabetic retinopathy, which was monitored in an ophthalmology clinic. At her mid-trimester scan the fetus was found to have bilateral hydronephrosis that was monitored with serial scans and remained stable. In the third trimester the fetal abdominal circumference was elevated above the 90th centile but all other parameters, including liquor volume, were within normal limits. This was compatible with a third trimester HbA1c of 49 mmol/mol and was considered to be reflective of the patient's inadequately controlled diabetes. At 30+3 weeks she developed pregnancy-induced hypertension and was started on methyldopa 250 mg three times daily with regular community monitoring.

INVESTIGATIONS

She was subsequently referred from antenatal clinic at 31+6 weeks with proteinuria and hypertension. On admission she was found to have a significantly raised 24 hours urine protein level of 0.61 g/24 hours (<0.3 g/24 hours is the upper limit of normal in pregnancy) and consistently high blood pressure (>150/90 mmHg). Initial blood monitoring showed normal liver function, haemoglobin and platelets with overall normal biochemistry in the context of pregnancy (table 1). She was diagnosed with pre-eclampsia and managed as an inpatient on the antenatal unit. Antihypertensive treatment was optimised with the addition

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Table 1 Trend of blood investigations

Day of admission	1	2	3	4	5	6	7	8	9	10	11	12	13	14 (delivery)	15
Sodium (mmol/L)	130	128	115	118	121	122	124	128	129	124	125	129	131	127	138
Potassium (mmol/L)	4.4	4	5.8	4.7	4.5	5.1	5	5	4.1	5	5.1	4.9	5.1	5.5	4.6
Urea (mmol/L)	2.4	2.6	4	3.5	3	2.7	3.3	3.7	3.2	6.3	6.3	6.3	7.3	7.7	2.9
Creatinine (µmol/L)	55	53	56	60	62	57	57	63	58	59	56	55	60	63	54
Alanine aminotransferase (IU/L)	7	7	6	6	7	13	16	22	35	50	52	49	48	32	33
pH*				7.44	7.42	7.41	7.42	7.45	7.45	7.42					
HCO_3^-* (mmol/L)				18.3	18.3	20.3	21.4	20.2	22.9	21.4					
Base excess*				−5.9	−5.9	−4.3	−3.1	−3.8	−1.1	−3.1					
Lactate (mmol/L)*				1.4	1.4	1.0	1.2	1.0	1.0	1.6					
Glucose (mmol/L)*				8.0	8.0	9.7	6.1	8.1	8.1	8.7					

*Denotes from arterial blood sampling.

of labetalol 200 mg three times a day and she received intramuscular steroids for fetal lung maturity in anticipation of a potential premature delivery for maternal well-being. As steroid administration is known to disturb normal glycaemic control, a variable-rate insulin infusion was commenced.

On day 3 of admission she became increasingly symptomatic with severe headaches, nausea and visual disturbance. Repeat bloods demonstrated a significant decrease in her plasma sodium to 115 mmol/L in contrast to otherwise stable markers of pre-eclampsia (normal range in pregnancy=130–140 mmol/L)[4] . Plasma osmolality was found to be decreased at 249 mOsm/kg (normal range=280–300 mOsm/kg), with a raised urinary osmolality of 716 mmol/kg and urinary sodium of 124 mmol/L (in the context of hyponatraemia normally <100 mOsm/kg and <20–40 mmol/L, respectively).

DIFFERENTIAL DIAGNOSIS

Our patient was assessed to be clinically euvolaemic with inappropriately high urinary osmolality and sodium levels. Her cumulative fluid balance was positive 3 L and she had a urine output of 50–100 mL/hour. Her serum lipid, protein and glucose levels were normal. Differentials in such a case would include an endocrine pathology such as hypothyroidism or Addison's disease, both not uncommon with a history of type 1 diabetes mellitus (figure 1). This was excluded as cortisol and thyroid profiles were found to be normal. Based on the fluid status, urinary studies, osmolalities and normal endocrine profile, a working diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) was made at this stage.

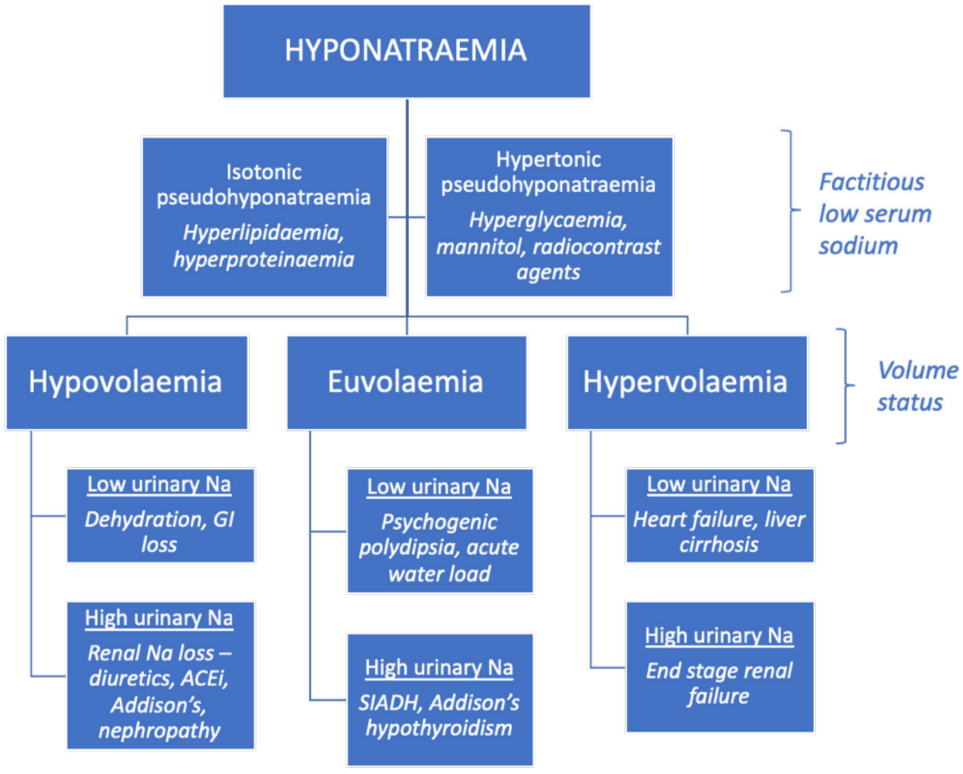


Figure 1 Aetiology of hyponatraemia according to volume status and urinary composition. Adapted from Spasovski *et al*.[28] ACEi, ACE inhibitor; GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone.

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TREATMENT

She was transferred to the intensive care unit (ICU) for serial arterial blood gas monitoring and central venous access for further management. A catheter was inserted to strictly monitor fluid input/output and electrolytes were measured with 3 hourly blood gases. She was cautiously fluid restricted by 1 L/24 hours and sodium was supplemented with 150 mL boluses of hypertonic saline 1.8%–3.0% over 10–20 min as required. Caution was taken not to correct her plasma sodium by >10 mmol in the first 24 hours.

On the second day of her admission to ICU, she developed an acidosis with a base excess of −5.9 in the absence of lactataemia. She was found to have a capillary ketone level of 3.6 mmol/L but glucose levels within normal range and was subsequently managed for a euglycaemic ketoacidosis with a 'dry' variable-rate insulin infusion (without the administration of dextrose-containing fluid).[5] She had an average urine output of 50–100 mL/hour with 24 hours fluid balance of −900 mL and her plasma sodium had risen to 121 mmol/L. Intravenous broad-spectrum antibiotics were commenced following a positive urinary dipstick with the concern that infection and sepsis had triggered the acidosis. She was managed for a total of 7 days on ICU until her ketoacidosis and hyponatraemia had resolved. From here she was stepped back down to the antenatal unit.

OUTCOME AND FOLLOW-UP

On stepdown the patient developed progression of her pre-eclampsia, associated with lability in her blood pressure and a rise in hepatic enzymes. Her alanine aminotransferase was 52 IU/L (normal range for third trimester=6–32 IU/L) but haemoglobin and platelets were within normal range.[4 6] She was transferred to a room on the labour ward for one-to-one monitoring with ongoing joint ICU/obstetric care and worked up for an induction of labour at 33+3 weeks for worsening pre-eclampsia. She received 2 mg dinoprostone per vaginam and delivered after 18 hours via forceps. Her postpartum recovery was complicated by a return to theatre for management of major obstetric haemorrhage with manual placental removal and perineal repair and a total estimated blood loss of 1450 mL.

At day 1 post partum her sodium had normalised to 138 mmol/L. She remained in hospital for a few days post partum for blood pressure control with a few further instances of hypertension but no long-term physical sequelae.

DISCUSSION

This case demonstrates the significant impact that hyponatraemia may have on the presentation and management of PET. This was first reported in 1970 and has been followed by only a handful of cases.[7–27] To the best of our knowledge, the combination of hyponatraemia and pre-eclampsia in the context of type 1 diabetes mellitus has only been reported once previously.[15]

Osmolality and volume status are maintained by the action of both antidiuretic hormone (ADH) and the renin-angiotensin-aldosterone system. Increased plasma osmolality stimulates the release of ADH in the posterior pituitary, which acts renally to increase water re-absorption and balance serum osmolality. Low plasma osmolality usually inhibits this pathway but in the context of volume depletion, ADH is released even in a hypo-osmolar state. Hyponatraemia may be a spurious biochemical finding caused by the effect of lipid, protein and other agents on plasma constitution (figure 1).[28] Causes of true hyponatraemia are categorised by clinical volume status and urine sodium concentration. In previous cases of hyponatraemia occurring in pre-eclampsia, this assessment provides variable hypotheses for aetiology; in some patients, a hypervolaemic status of toxaemia was deemed the cause of a 'dilutional' hyponatraemia. This may be compounded by high levels of protein loss meeting the criteria for nephrotic syndrome.[20 21] SIADH has been tentatively concluded as the cause of low plasma sodium in several reports with a similar profile of low serum osmolality and high urinary sodium in the context of euvolaemia.[7 10–12] In our case, however, a working diagnosis of SIADH was significantly complicated by the sequelae that evolved.

Pregnancy and hyponatraemia

Pregnancy presents a unique predisposition to hyponatraemia with physiological and hormonal changes in the first 8 weeks' gestation that affect osmoregulation. This phenomenon, known as 'pregnancy-induced osmostat reset', normally results in a decrease in plasma sodium concentration of 5 mmol/L that is stable throughout pregnancy.[29] Oxytocin and ADH are released during uterine contractions and in response to pain, nausea and stress. This may be the cause of a moderate hyponatraemia that is sometimes seen during labour. In addition, oxytocin will potentiate the action of ADH as is demonstrated by the administration of synthetic oxytocin that often leads to iatrogenic hyponatraemia.[30]

Pre-eclampsia and hyponatraemia

Previously reported cases have proposed that a dysfunctional placental unit and altered hormone profile in pre-eclampsia can lead to an SIADH-like syndrome.[9] The pathological immune response to placental insufficiency has been associated with a reduction in circulating plasma volume, which is a stimulus for ADH release.[31] It has been postulated that there is an alteration in vasopressinase activity and increase in receptor sensitivity in the pre-eclamptic placenta.[32 33] This may lead to high levels of ADH secretion while also enhancing the ADH effect of intrapartum oxytocin secretion.

Diabetes and hyponatraemia

Our case brings into consideration a further complexity; the management of hyponatraemia in a patient with diabetes with pre-eclampsia (figure 2). Diabetes mellitus affects 5% of all pregnancies globally, with increasing rates of type 1 and type 2 pre-gestational diabetes in recent years. Women with pre-existing diabetes are at a vastly increased risk of developing pre-eclampsia in the antenatal period with incidence reaching 15%–20% in type 1 diabetes versus 2%–7% of women without diabetes.[34 35] Low plasma sodium levels are often seen in poorly controlled diabetes as osmolality is complicated by lability in blood glucose. Extracellular glucose attracts water via osmosis leading to a dilutional hyponatraemia.[36] In addition to this, it is well established that insulin exerts an antinatriuretic effect on the kidney and therefore a deficiency may lead to salt wasting and lowered plasma sodium.[37]

Managing hyponatraemia becomes particularly challenging in the case of hyperglycaemia or ketoacidosis in diabetes. Ketone bodies potentiate urinary electrolyte losses and renal sodium wasting and thus can cause hyponatraemia.[38] In our case, the lack of hyperglycaemia associated with diabetic ketoacidosis may have resulted in an initial delay in recognition

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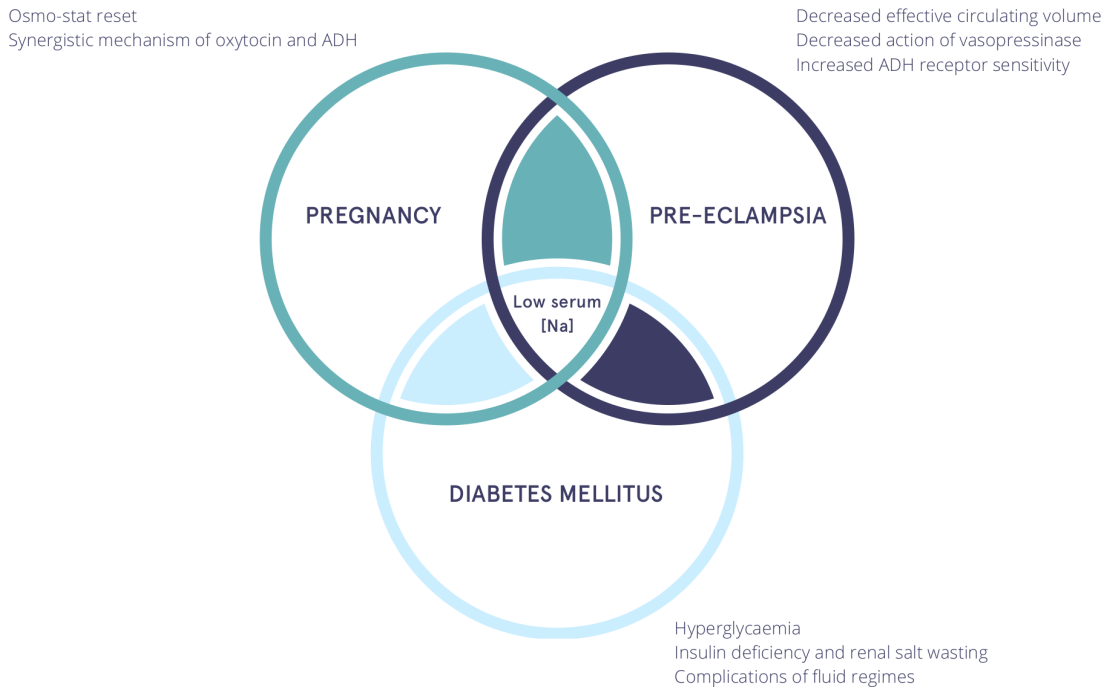


Figure 2 Schematic to represent the interplay of factors contributing to hyponatraemia in patient with pre-eclampsia, diabetes. ADH, antidiuretic hormone.

and therefore it is difficult to disentangle the contribution of this from the initial working diagnosis of SIADH. Furthermore, standard management of diabetic ketoacidosis in adults involves large volume fluid administration that may exacerbate hyponatraemia. This poses a risk in patients with concurrent pre-eclampsia as well as other conditions of fluid overload such as cardiac and renal failure. Unfortunately, there is very little guidance to advise fluid management in these cases other than 'using caution' alongside close monitoring.[39] Reference has been made to 'dry' insulin infusions without large volumes of substrate, for example the use of 10% glucose at a reduced rate of administration.[5] This was the approach that was opted for in our case to reduce the opposing risks of fluid overload and hypoglycaemia.

Treatment of hyponatraemia in pregnancy

The onset of hyponatraemia in our patient was thought to be associated with headache and nausea, symptoms that are also commonly reported in pre-eclampsia. In fact, the presentation of severe acute hyponatraemia may be clinically indistinguishable from eclampsia with an extremely similar spectrum of neurological symptoms including weakness, convulsions and coma due to cerebral oedema.[40] In the hospitalised population hyponatraemia is associated with an increased all-cause mortality, independent of clinical variables.[41] The presentation of hyponatraemia is further complicated in the pregnant woman as the electrolyte imbalance is directly passed onto the fetus.[42] This can increase the risk of neonatal jaundice, transient tachypnoea of the newborn and neonatal seizures. For this reason, severe hyponatraemia should be treated as soon as possible to achieve incremental improvements.

The development of hyponatraemia in our case was multifold and this has significant implications for management. It is to be noted that, at present, nationally accepted guidance for management of electrolyte derangement in pregnancy, let alone in the context of pre-eclampsia, does not exist. In the presence of symptoms and/or an acute drop in plasma sodium concentration (defined >10 mmol/L within 24 hours), the European Society of Endocrinology guidelines recommend correcting the sodium level immediately.[28] This can be achieved with small titratable intravenous boluses of 1.8%–3% hypertonic saline. The correction must not exceed >10 mmol/L per 24 hours so as to avoid the potentially fatal complication of central pontine myelinolysis.[43] Further management focuses on comprehensive assessment and cause-specific treatment. In the case of SIADH, fluid restriction of 500–1000 mL/day is usually recommended. Demeclocycline, a tetracycline-derived ADH antagonist, may be used for severe refractory cases, however this drug is currently contraindicated in pregnancy.[44] If hyponatraemia is associated with pre-eclampsia it would seem reasonable that urgent fetal delivery is considered. However, this decision must be carefully weighed up against

Learning points

- Hyponatraemia may be associated with pre-eclampsia and can have devastating consequences for both mother and baby.
- Specific and focused monitoring of plasma sodium levels may be helpful in the optimum management of women with severe pre-eclampsia, particularly when compounded by diabetes mellitus.
- Intravenous small volume bolus sodium correction and fluid restriction are appropriate management strategies for hyponatraemia in the context of pregnancy and pre-eclampsia, however fluid management must be balanced with the requirements of comorbidities, such as diabetes mellitus.

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the risks of preterm delivery such as fetal respiratory distress syndrome and hypoxic ischaemic encephalopathy as well as the vulnerability of the neonate inheriting a severe electrolyte derangement. To reduce the risk of the complications of preterm birth, it is recommended to consider administration of corticosteroids.[45] In this case the team and patient opted to achieve maternal resuscitation and normalisation of plasma sodium levels prior to delivery but an early delivery could not be avoided following this due to evidence of worsening pre-eclampsia.

Conclusion

Our case demonstrates a complex, multi-factorial presentation that has been previously under-evaluated. The hormonal and biochemical alterations of pregnancy that predispose to hyponatraemia and can be compounded by pre-eclampsia and type 1 diabetes mellitus present a mixed picture that sometimes demands opposing therapeutic strategies. Further reporting and research is necessary to determine the optimal management to prevent potential maternal and fetal morbidity and mortality but it is clear that close monitoring, correction and carefully considered fluid management are required.

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