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Teaching Point
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A pregnant woman with *de novo* polyuria-polydipsia and elevated liver enzymes

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Case

A 32-year-old black woman, gravida 1, para 0, was admitted in our hospital in her 29th week of a gemellar pregnancy because of the risk of preterm delivery and suspicion of pre-eclampsia. The patient's pregnancy had been uneventful until her hospitalization and no previous history of gestational diabetes or hypertension was elicited. The patient's past medical history was unremarkable. Weight gain during pregnancy had been appropriate and serial ultrasounds had demonstrated adequate growth of both fetuses. On admission, she complained of right abdominal pain but reported no fever, vaginal bleeding or discharge, headache, blurry vision or oedema. Physical examination revealed an afebrile patient with normal skin turgor, and a tender but not enlarged liver. Her blood pressure was 100/70 mmHg, and pulse 80 beats per minute. An abdominal ultrasound showed a gemellar pregnancy with normal amniotic fluid, a normal hepatic size and appearance, and a slight distension of the urinary tract. The patient was kept under observation. Laboratory values at entry showed an elevation in liver-function tests, uric acid and creatinine levels (Table 1). Haemoglobin, platelet count, coagulation and thyroid function studies, as well as potassium, calcium and glycaemia levels were within normal range. HIV as well as hepatitis serologies were negative. A urine culture remained sterile. A presumptive diagnosis of acute fatty liver of pregnancy was made.

From days 2 to 9 of hospitalization, the elevation of the liver enzymes, and uric acid level persisted, but without significant exacerbation (Table 1). Creatinine clearance was 99.6 ml/min. Maternal blood pressure and fetal evaluation remained normal. On day 9, the patient developed a syndrome of polydipsia and polyuria. These symptoms had been appearing the day before admission but the patient didn't mention them at entry. A first recorded urine output was 5.0 l/24 h with a specific gravity of 1002. On day 11, urine output was 8 l, plasma osmolality 290 mOsml/kg and urine osmolality 60. Since glucose, potassium and calcium levels were normal, a diagnosis of diabetes insipidus (DI) was retained.

8-D-arginin vasopressin (dDAVP) was not introduced since the course of pregnancy was marked, some hours later, by a premature rupture of the membranes with rapid labour initiation. Two healthy female babies weighing 1630 and 1650 g were delivered vaginally without complication, at 31 2/7 weeks. The patient delivered a placenta 1.5 times (640 g) the expected weight for the gestational age. Post-partum, the patient nursed her babies normally. On day 13 (1 day after delivery), the plasma level of arginin vasopressin (AVP) was 0.6 pg/ml (normal values 0.2–2.5 pg/ml). Symptoms of polyuria-polydipsia and laboratory abnormalities regressed rapidly after delivery (Table 1). Plasmatic and urinary osmolality measured 3 months after delivery, with the patient being asymptomatic, were within normal range (Table 1). The final diagnosis was transient DI of the pregnancy, probably mediated by an excessive activity of placental vasopressinase, and associated with acute fatty liver.

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Discussion

Pregnancy is associated with physiological osmoregulatory changes. To explain this well recognized phenomenon, two mechanisms have been put forward: a resetting of the osmotic threshold, i.e. the set-point for plasma osmolality at which pregnant women experience thirst and release AVP, and the placental release of a cysteine-aminopeptidase (vasopressinase), an enzyme that rapidly inactivates AVP. The lowering of the osmotic threshold leads to a decrease of the plasma osmolality by ~10 mOsm/kg at 10 weeks of pregnancy, after which a new steady state is maintained until term [1]. Thus, AVP release is not suppressed at the usual levels of tonicity and free water is retained, causing a fall in plasma sodium concentration by ~5 meq/l. Despite the increase in the clearance of AVP due to vasopressinase effect, AVP plasma concentrations remain unchanged, suggesting a compensatory increase in secretion to maintain fluid balance.

DI is generally caused either by failure of AVP secretion (central DI) or by resistance of the renal collecting duct to AVP (nephrogenic DI). Central DI may occur secondary to pituitary or brain tumours, infiltrative diseases such as sarcoidosis or histiocytosis, after trauma, surgery or rupture of intracranial aneurysm, or be idiopathic [2]. Nephrogenic DI can be congenital or acquired, linked with chronic interstitial nephritis, potassium deficiency or hypercalcaemia, or related to drugs [2]. During pregnancy, and in the absence of glycosuria, hypokalaemia or hypercalcaemia, DI can be established if a patient with a syndrome of polyuria-polydipsia has a serum osmolality > 285 mOsm/kg associated with persistent hyposthenuria (Table 2) [1,3]. DI can be confirmed by a hypertonic saline infusion or a water deprivation test (Table 3). Women with DI will not concentrate their urine osmolality, in contrast to women with psychogenic polydipsia. However, dehydration is problematic in pregnancy because the resulting decrease in plasma volume may lead to utero-placental insufficiency [4]. Therefore, a water deprivation test should be performed only if signs of polyuria or polydipsia persist more than 6 weeks post-partum.

In pregnant woman, the classical central or nephrogenic DI should be distinguished from *de novo* transient DI (gestational DI), a third category of DI which appears in late pregnancy and resolves in the very first weeks after delivery, as illustrated in our case report. On the basis of clinical and physio-pathological characteristics, at least two forms of gestational DI should be distinguished [1], apart from a form of DI appearing early after delivery probably caused by Sheehan's syndrome [2]: (i) in patients with previously unrecognized partial central DI, with sufficient hormone secretary capacity to escape detection when non-pregnant, the increased metabolic clearance rate due to the vasopressinase activity during pregnancy will lead to DI. This form should be sensitive to AVP. (ii) The form called transient AVP-resistant DI is due to excessive degradation of seemingly unaltered secretion of AVP, due to increase in vasopressinase activity.

Vasopressinase is a cystine aminopeptidase elaborated by placental tissue (trophoblast), which inactivates AVP, oxytocin, and some other small peptides, by sequentially cleaving amino acids from the N-terminus [1]. Its physiological function remains however unclear. Vasopressinase activity increases by 1000-fold from week 4 to 38 of gestation, remains elevated until

Table 2. Major causes of polyuria during pregnancy

Water diuresis	Solute diuresis
Primary polydipsia	Hyperglycaemia
Central DI	Mannitol
Nephrogenic DI	Post-obstructive diuresis
Transient DI	Saline loading
Hypercalcaemia	Salt losing nephropathy
Hypokalaemia	
Lithium	
Interstitial diseases	
Sickle cell anaemia	

Table 1. Laboratory data

	Entry	Day 5	Day 11	Day 12 (delivery)	Day 14	Day 90
Blood						
Na (mmol/l)	141	140	140		139	138
Creatinine (μmol/l)	100	90	101		81	82
BUN (mmol/l)	3.4	3.8				
Osmolality (mOsm/kg)	281		290			286
Uric acid (μmol/l)	496	557	514		353	
ASAT (U/l)	111	125	120		53	
ALAT (U/l)	122	138	116		67	
LDH (U/l)	522	555			466	
AP (U/l)	218	238	242		201	
Bilirubin (μmol/l)	< 10	< 10	< 10			
Urine						
Osmolality (mOsm/kg)			60		136	754
Proteinuria (g/l)	0.02	0.04			0.05	
Volume (l/24 h)			8.0		4.4	1.4

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LDH, lactate deshydrogenase; AP, total alkaline phosphatases.

Table 3. Water-deprivation, AVP and dDAVP test during pregnancy

	Urinary osmolality with water deprivation (mOsm/kg H_2O)			Plasma AVP (pg/ml) after water deprivation
	Elevation in urinary osmolality with AVP		Elevation in urinary osmolality with dDAVP	
Normal	> 800	> 2	Little or no increase	Little or no increase
Complete central DI	< 300	Undetectable	Partially or substantially increased	Substantially increased
Partial central DI	< 300–500	< 1.5	Partially or substantially increased	Substantially increased
Transient AVP-resistant DI	< 300–500	< 1.5	No increase	Substantially increased
Nephrogenic DI	< 300–500	> 5	Little or no increase	Little or no increase
Primary polydipsia	> 500	< 5	Little or no increase	Little or no increase

Modified from Lanese and Teitelbaum [11].

delivery, than decreases at a logarithmic rate of 25% a day post-partum, having virtually no activity by the 12th post-partum day. The release of vasopressinase results in an ~4-fold increase in AVP catabolism rate, which requires a compensatory synthesis to maintain AVP plasma concentration and fluid balance unchanged [1]. Serum vasopressinase activity is proportional to the weight of the placenta, explaining that in multiple pregnancies, an increased plasma vasopressinase activity is encountered [5]. The site of vasopressinase metabolism is not known, but is likely to take place in the liver. After delivery and placental removal, vasopressinase levels decreased rapidly, resulting in normalization of the fluid balance, and consequent resolution of the DI.

Administration of AVP can differentiate the two forms of gestational DI (Table 3) [3]. In central sub-clinical DI exacerbated during pregnancy, urine should concentrate within an hour after administration of AVP i.m., in contrast to transient AVP-resistant DI. However, most central sub-clinical DI respond only partially to AVP since part of the exogenous AVP is degraded by normal levels of vasopressinase. If the urine still does not concentrate 2 h after AVP administration, dDAVP, an AVP analogue with a different N-terminus that renders it resistant to the vasopressinase action, may be given [6]. Both forms of transient DI are exquisitely responsive to dDAVP which constitutes the treatment of choice. In the 17 cases reviewed by Krege *et al.* [3], only dDAVP successfully established anti-diuresis. Women with complete central DI require more exogenous AVP to control polyuria during pregnancy, probably because of the increased clearance of AVP due to increased vasopressinase activity, and present a gradual return of their usual replacement doses in the post-partum period [7]. Pre-existing symptomatic central DI should therefore be treated with dDAVP during pregnancy. No adverse maternal or fetal effects from dDAVP use during pregnancy have been reported [6]. Moreover, dDAVP has no pressor effect which is important in view of transient DI associated with pre-eclampsia.

One recent important finding, in the majority of women with transient DI of the pregnancy, is the simultaneous occurrence of anomalies of the liver-function tests. Krege *et al.* [3] reviewed reports of 17 women with transient DI and found associated abnormal liver tests in 16 of them (in one case liver functions were not reported). Moreover, they found a diastolic blood pressure $\geq$90 mmHg in 12 patients, proteinuria > 250 mg/24 h in six of them, and elevated uric acid levels in 12 cases (not reported in five). One woman had recurrence of the DI in a subsequent pregnancy [3]. In another study, Kennedy *et al.* [4] reported six cases of transient DI of the pregnancy in association with abnormal liver tests and biopsy-proven acute fatty liver of pregnancy. Five out of six were primigravida. Elevated blood pressure (> 140/90 mmHg), without significant proteinuria, was present in four of them. There was an increase in uric acid levels (> 400 μmol/l) in all but one patient. Three women have since had uneventful pregnancies. Recently, Hamai *et al.* [8] reported six cases of DI during pregnancy, and observed that pregnancies in which clinical symptoms of DI became apparent were associated with hypertension and abnormal biochemical data compatible with pre-eclampsia, whereas pregnancies preceded by DI were uneventful as long as dDAVP was appropriately administered.

To explain the association of DI with elevated liver function tests, one advanced hypothesis is that acute liver dysfunction could impair degradation of vasopressinase, thereby extending vasopressinase half-life activity, resulting in greater clearance of AVP. It has been suspected that pre-eclampsia associated with excessive vasopressinase activity might be explained if the products of AVP degradation by vasopressinase retained pressor activity, even after anti-diuretic activity has been destroyed. However, Gordge *et al.* [9] have shown in a recent study that AVP degradation products had no significant pressor activity and are therefore unlikely to be pathogenic in hypertensive pregnancy. An important point is that pregnancies in women with transient DI should be considered at high risk because of the potential to develop pre-eclampsia, or fatty liver. Moreover, the manifestations of DI, i.e. diluted and abundant urine output, may mask emerging severe pre-eclampsia.

In our patient, a *de novo* syndrome of polyuria-polydipsia associated with hepatic, uric acid, and renal function abnormalities developed during the third trimester of pregnancy, while glycaemia, potassium and

calcium levels were in the normal range. It was characterized by slightly elevated plasmatic osmolality, hypernatraemia and hyposthenuria. The increase of uric acid and creatinine plasma levels was attributed to a probable pre-renal component. Prior to the liver-function test abnormalities, our patient had neither hypertension nor proteinuria, excluding the diagnosis of pre-eclampsia. A toxic, pharmacological, or viral cause to the elevated liver enzymes was ruled out, and a diagnosis of fatty liver of pregnancy was at this state the most probable diagnosis [10]. The rapid amendment of the symptoms and of laboratory abnormalities after delivery, was consistent with a transient DI of the pregnancy. The gemellar nature of the pregnancy that could induce excessive vasopressinase activity, and the hepatic dysfunction (acute fatty liver) which could reduce the catabolism of vasopressinase were consistent with an AVP-resistant DI of the pregnancy. The normal plasma AVP level 1 day after delivery (0.6 pg/ml), and an urinary osmolality spontaneously above 750 mOsm/kg 3 months post-partum render unlikely the diagnosis of a partial central DI. This case and others previously reported demonstrate that transient DI appears to be associated with gemellar pregnancy, pre-eclampsia or acute fatty liver [3,4,8].

Teaching points

Transient DI of pregnancy can occur in the third trimester and disappears rapidly post-partum. It is associated with gemellar pregnancy, pre-eclampsia or acute fatty liver. There are two distinctive forms—the central sub-clinical and the AVP-resistant DI. Both forms respond to dDAVP.

Conflict of interest statement. None declared.

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