Gestational Diabetes Insipidus in a 21 year-old G2P1 with Twin Pregnancy

Marbert John T. Cardino, M.D. and Iris Isip-Tan, M.D.

Abstract

Background: Transient diabetes insipidus (DI) is an uncommon pregnancy-related condition which results from the excessive placental vasopressinase activity. This is a rare condition occurring in 2-4/100,000 deliveries.

Clinical Presentation: Our patient consulted for bilateral lower extremity weakness and polyuria. A similar condition was described during her first pregnancy.

Diagnosis: Thirteen liters of urine was collected on the first hospital day. She had a dilute urine with a specific gravity of 1.005. This was confirmed with a low 24 hour urine osmolarity (175mosm/L) and a correspondingly high serum osmolarity (320 mosmol/K). She had a normal 100 grams OGTT and renal ultrasound. These were consistent with gestational DI. Significant proteinuria, elevated liver transaminases and hypertension were noted. Diagnosis can be done by doing a water deprivation test but is potentially dangerous to both mother & fetus. On the 15th day, she delivered vaginally. Urine output was decreasing until the 12th postpartum day when it reverted back to normal. However, the 12th postpartum day water deprivation test was consistent with a partial nephrogenic diabetes insipidus. A normal water deprivation was documented 6 weeks later reflective of the normalization of the kidney’s concentrating ability.

Significance: Transient AVP resistant DI should be considered in pregnant patients presenting with polyuria. Early recognition is warranted, as significant co-morbidities are associated with it. Usually symptoms set in during the 20th gestational week because the vasopressinase activity is maximal at this time. Pregnancy unmask this condition in subclinical central DI because it lowers the osmotic setpoint, and decreases the renal responsiveness to AVP.

Conclusion: Judicious hydration and vasopressin replacement should be considered upon the diagnosis to prevent maternal and fetal compromise.

Keywords: polyuria, gestational diabetes insipidus, vasopressinase

Case Presentation & Review of Related Literature

We report a case of a 21 year-old pregnant patient admitted for progressive lower extremity weakness which started a week prior to admission following 5 days of vomiting at least 1-2 cups per episode. Weakness was initially described to be difficulty in standing up from a sitting position, which later on progressed to inability to move both lower extremities in a span of one week only. Prior to this episode, patient noted polyuria of least four liters a day a month prior to admission. This was associated with polydipsia which she neglected believing it was part of the pregnancy as she described a similar episode during her first pregnancy sometime at the 5th month of gestation.

She had her menarche at 15 years old and subsequently had regular menstrual period of 5-7days duration consuming 3-4 soaked pads per day. At the time of admission, she was 23 6/7 weeks age of gestation with twin pregnancy.

On review of history, patient had a normal first pregnancy. There was no excessive bleeding. Complete resolution of polyuria-polydipsia was noted postpartum. She was non-hypertensive, non-diabetic, and non-asthmatic. She had no family history of hypertension and diabetes.

On physical examination, she was hypertensive with blood pressure of 150/90, heart rate of 90/minute. She had essentially normal physical examination findings except for the motor exam. Both lower extremities were graded 1/5, with intact pain sensation. There were no visual field cuts and papilledema on fundoscopy. Other neurological findings were normal. On review of systems, patient had no thyromegaly, blurring of vision, and photophobia. There were two fetal heart beats auscultated at the right lower and upper quadrants of the abdomen.

Polyuria is described as urine output of more than three liters a day. In the work-up of a polyuric pregnant patient, it is important to determine whether this is a solute or a water diuresis especially that the hormonal environment of a pregnant patient predisposes them to develop diabetes mellitus. We can only differentiate this by getting a 24 hour urine osmolarity.

On admission, the patient had a urine output of 13 liters in a day with a specific gravity of 1.005 and a 24 hour urine osmolarity of 175mosm/K. The results were consistent with water diuresis. The serum sodium was 155 mmol/L and serum

1Fellow-in-training, Section of Endocrinology, Diabetes and Metabolism, University of the Philippines-Philippine General Hospital
2 Consultant, Section of Endocrinology, Diabetes and Metabolism, University of the Philippines-Philippine General Hospital
osmolarity of 311 mosm/K. Please refer to the Table 1 above for the urine output, urine osmolarity, serum electrolytes, and serum osmolarity of the patient before delivery.

In a pregnant patient, the common causes of solute diuresis are salt losing nephropathy, mannitol use and diabetes mellitus.1 Gestational diabetes mellitus was excluded. The 50 grams oral glucose challenge test was 145mg/dl. A definitive 100 grams oral glucose tolerance test (OGTT) was done with the following results: fasting glucose of 76mg/dl, 1st hour value of 96mg/dl, 2nd hour value of 99 mg/dl, and 3rd hour value of 117 mg/dl. She had no family history of diabetes, and no history of delivery of large baby. Based on the American Diabetes Association2, the above values for the 100 grams OGTT were all normal.

For water diuresis, the common causes are central diabetes insipidus, nephrogenic diabetes insipidus, primary polydipsia, hypokalemia, hypercalcemia and lithium use.1 Looking at the above determinations, our patient had water diuresis with a urine output of >40cc/K, low urine specific gravity of 1.005, low urine osmolarity of 175mosm/K, high serum sodium (155 mmol/L) and high serum osmolarity of 311 mosm/K. In a pregnant patient, a serum sodium of 155 mmol/L is already considered high. According to Brewster3, pregnancy is a state of water retention in preparation for delivery. There is a decrease in the osmotic threshold beginning at the 10th week of gestation leading to decrease in the serum osmolarity by 10mosm/K and a new steady state is maintained thereafter. Because of this, the serum sodium decreases by 5mmol/L from the lower normal cut-off, making it at 130 mmol/L. The osmostat is reset at 270mosm/K from 280mosm/K in a non-pregnant patient.2 The normal thirst threshold decreases to 287mosmol/K from 298 mosmol/K in a non-pregnant patient.2 The physiologic basis for this reset osmostat is not clear. Recent experiments in humans have shown that human chorionic gonadotropin injection in a non-pregnant women lowers their osmostat by 5mosm/kg.3

The clinical criteria for the diagnosis of diabetes insipidus is a urine output of >40cc/K and a 24 H urine osmolarity of <250mosm/K which were compatible with our patient’s results. Our patient did not have symptoms suggestive of a space occupying lesion making the consideration of central DI less likely. There was no history of difficult delivery of her first child which may predispose our patient to have Sheehan’s syndrome. There were no visual field cuts and fundoscopic findings were all normal. Hypercalcemia, hypokalemia, low protein diets and sudden release of a ureteral obstruction are the acquired causes of nephrogenic diabetes insipidus.4 According to Sands4, the polyuria in these cases is not as severe as in central diabetes insipidus and congenital nephrogenic diabetes insipidus. Above factors are known to down regulate the aquaporin (AQP2) protein in the renal medulla of rat kidneys.5 Hypokalemia and release of ureteral obstruction decrease the urea transporters (UT-A1, UT A-2, UT-B) in rat kidneys.6 These factors aggravate the loss of concentration capacity of the kidney. These factors may have aggravated the polyuric state of the patient. As we shall see, following the correction of the hypokalemia in this patient there was a decreasing trend in the urine output. Ultrasound of the kidneys showed a bilateral ureteropelvicectasia, no urinary stones, and the right kidney measured 12.5 cm X 7.5 cm X 5.9 cm with 1 cm cortical thickness and the left kidney measured 12.3 cm X 5.2 cm X 5.9 cm with cortical thickness of 1 cm. A third etiology had been described in the pregnant patient known as the gestational diabetes insipidus. This is a rare condition occurring in 2-4 cases per 100,000 deliveries.7 It was Barron (1984) who first fully-described this condition in 3 pregnant patients with polydipsia-polyuria symptoms occurring in the 2nd-3rd trimester of pregnancy. The mechanism of occurrence of this entity is attributed to the vasopressinase activity

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<th>Hospital Day</th>
<th>Urine Output cc/K (urine)</th>
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<th>Serum Na</th>
<th>Serum Osmolarity</th>
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elaborated by the placental trophoblast and reaches maximal activity sometime during the 22nd to 24th week of gestation. The vasopressinase is a cystine aminopeptidase which increases the catabolism of vasopressin four-folds. Its activity is proportional to the placental weight. In our case, she had twin pregnancy and the polyuria-polydipsia symptoms occurred during the 22nd week of gestation. She described a similar condition in her first pregnancy occurring sometime during the 5th month of pregnancy with complete resolution postpartum, compatible with the profile of gestational diabetes insipidus.

There are two known mechanisms for the occurrence of gestational DI. First, it may occur in patients with subclinical central DI which maybe unmasked by the pregnancy state. Second, it may occur in multifetal pregnancy because the vasopressinase activity is proportional to the placental weight. The mechanisms of unmasking a subclinical central DI in pregnancy are as follows: decrease in the osmotic set point, decrease in the serum sodium, decrease in the thirst setpoint, decrease in the renal responsiveness to vasopressin and increase in the vasopressinase activity. The vasopressinase activity is identified as a common etiology in both scenarios.

Other problems identified in our patient were the occurrence of the hypertension and the elevated liver enzymes. Our patient had a blood pressure range of 120-130/70-80, maximum of 160/90 and she was on Methyldopa 500mg three times a day with apparent good control. She had a 24 hour urine protein of 3 grams per day. Serum alanine aminotransferase was 229 IU/ml and aspartate aminotransferase of 249 IU/ml (4X the upper limit of normal). Serum LDH was also high at 334 mg/dl. These parameters were associated with gestational DI. Acute liver dysfunction is associated with gestational DI. The vasopressinase is metabolized in the liver and the liver dysfunction may have prolonged the half-life of the vasopressinase predisposing to concentration inability, which is compatible with this case. Barbey and Krege showed association of hypertension and gestational DI. Barbey described 12 hypertensives among 17 patients with gestational DI, 16 with acute liver dysfunction of pregnancy and 6 with proteinuria. Sherer explained that the hypertension in these patients is caused by the retention of C terminus amino acids in the vasopressin which has the pressor activity since the vasopressinase only cleaves the N terminus amino acids. Our patient had all the circumstances that will describe the occurrence of gestational DI.

However during the 13-14th hospital day, the patient had flank pains and fever with a maximum of 39ºC. Septic work-up was done. Blood and urine cultures isolated Enterbacter cloacae. She was treated with Imipenem-Cilastatin for 2 weeks based on the sensitivity results. At that time, lupus nephritis and anti-phospholipid antibody syndrome (APAS) were entertained which may explain the concentrating inability, proteinuria, liver dysfunction and sepsis. Lupus work-up was done. Antinuclear antibody was negative with a normal C3 at 189 mg/dl (normal: 52-120mg/dl). Kaolin clotting time was 60 seconds (normal: 50-90 seconds), activated partial thromboplastin time at 36 seconds (normal: 25-40 seconds) and dilute russel viper venom time at 46 seconds (normal: 31-46 seconds) making the considerations of systemic lupus erythematosus and APAS not likely.

To differentiate the etiologies of gestational DI, a water deprivation test should be done however it is very risky in pregnancy because this may cause utero-placental insufficiency. This should be done only if symptoms persist 6 weeks postpartum. Barbey and Hamai instead suggested therapeutic trial with 1 microgram of synthetic vasopressin (desmopressin) and observe concentration of the urine among subclinical central DI. While in the transient AVP resistant DI described in multifetal pregnancy, administration of 1 microgram desmopressin will not concentrate the urine. In fact, in the later condition, the vasopressin levels are normal to slightly elevated because there will be a reflex increase in the vasopressin production because of the increase in vasopressin degradation, granting that these patients have normal hypothalamic and pituitary functions.

However during the 14th hospital day our patient delivered successfully two live baby boys 29 weeks of gestation. She had premature contractions triggered by the urinary tract infection.

During the first postpartum day, there was a drop in the urine output to normal levels and patient had normal thirst. According to Barbey, there is a logarithmic drop of the vasopressinase activity of about 25% on the first postpartum day and virtual absence of the vasopressinase activity on the 12th day postpartum. Please refer to the table below for the urine output, urine and serum electrolytes and osmolarity during the postpartum period.

At the 12th day postpartum, we expected virtual absence of the vasopressinase activity. As we shall see from the table above, the urine output was improving but the urine osmolarity remained low (<250 mosmol/K). During the first 4 days postpartum, there was still a urine output of > 40cc/K. At this point, the patient was still hydrated and blood transfusions were being administered. Because the urine osmolarity remained low at the 12th postpartum day, a subclinical central DI must be ruled out by doing the definitive water deprivation test. Water deprivation test is divided into 3 phases: preparation, dehydration and desmopressin phases. During the first phase, the patient was allowed free access to water overnight. Before the dehydration phase was started, a baseline weight, serum and urine osmolarities were taken. Thenafter, she was dehydrated for 8 hours. We had to weigh patient every 2 hours because if the weight loss is > 5% of baseline then the procedure will be aborted. After dehydration, 1 microgram of synthetic vasopressin was injected subcutaneously and patient was then allowed free access to water. Repeat serum and urine osmolarities were taken every 2 hours during the procedure. The results were as follows:

Normal individuals will show a gradual concentration of the urine osmolarity within 8 hours of dehydration but will
not further concentrate with administration of vasopressin. Complete central and nephrogenic diabetes insipidus show no concentration of the urine within 8 hours of dehydration however upon administration of vasopressin, patients with central diabetes insipidus will concentrate their urine but not with nephrogenic type. The results of our patient showed that there was an increasing trend in the urine osmolarity with water deprivation but suboptimal compared to healthy individuals and maybe consistent with a partial nephrogenic DI or a partial central DI. To differentiate them, administration of 1 microgram desmospressin increases the urine osmolarity by 200 mosm/K in partial central DI but not with the partial nephrogenic DI. Our patient had a partial response to the administration of desmopressin which was less than 200 mosm/K and therefore was consistent with a partial nephrogenic DI. Nephrogenic DI occurs in two scenarios. First, defects in the collecting ducts to respond to vasopressin and defects in the renal medullary interstitium to reabsorb water. Before delivery, the medulla was in a hypotonic state due to the pregnancy. The renal medullary interstitium takes approximately 6 weeks before a complete adaptation to its new extracellular milieu occurs. Thus a repeat water deprivation test was done 6 weeks postpartum.

After 6 weeks, our patient no longer complained of weakness and polyuria. She was able to sleep well at night and was not bothered with nocturia. She had a urine specific gravity of 1.015, ph 6.0, with absence of significant microscopic hematuria, proteinuria, and glycosuria. A repeat water deprivation test was done which showed normal results.

Clinical Significance
Diabetes insipidus is a syndrome characterized by excretion of abnormally high volume of dilute urine. Gestational diabetes insipidus (GDI) results from the increased metabolism of the AVP by the placental vasopressinase however, how much this increase in vasopressinase activity
contributes to the increased vasopressin clearance is not known. The signs and symptoms of gestational DI recur with subsequent pregnancies.

Judicious hydration and desmopressin replacement are the cornerstones of management in pregnant patients. Desmopressin is a synthetic vasopressin which is resistant to the vasopressinase action. The utility of desmopressin is both for diagnostic and therapeutic reasons. The dose generally utilized is 1 to 4 microgram per day. Symptomatic treatment is based on the slow correction of hypernatremia and osmolality. However, definitive therapy remains to be the delivery of the placenta.

We have to recognize this condition among pregnant patients presenting with significant polyuria to prevent maternal and fetal compromise. Neurologic manifestations encompassing from altered mentation to coma and seizures have been reported in pregnant patients unsuspected of having gestational DI who were subjected to nothing per os (NPO) during delivery. Mortality associated with hypernatremia in gestational DI is around 40-55% however it is unclear at present if hypernatremia is a cause or a marker of a severe disease. Treatment with desmopressin during the whole duration of pregnancy does not pose a major risk for the infant.

One of the twins succumbed to neonatal sepsis. The other twin was discharged improved after 2 months of hospitalization. Our patient had complete resolution of symptoms 6 weeks post-partum.

Conclusion

In summary, we presented a case of diabetes insipidus first diagnosed during the peripartum period which lead to a favorable maternal outcome however with poor neonatal outcome. Recognition of the condition is imperative to initiate judicious hydration and vasopressin replacement to prevent maternal and fetal compromise. Conditions associated with gestational DI like pre-eclampsia and acute fatty liver of pregnancy are reversible following the delivery of the placenta which is the definite therapeutic modality. We have to warn our patient for a possible recurrence in the subsequent pregnancies. Early recognition of this condition should be emphasized to prevent maternal and fetal compromise and to address the co-morbidities associated with the condition.

References