A Case of Subclinical Central Diabetes Insipidus Unmasked by Pregnancy

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Abstract
A 30-year-old woman was referred to our division because of polyuria and polydipsia, and was treated for transient diabetes insipidus associated with her pregnancy. At the time of consultation, the patient was at 34 weeks of gestation and being followed by an obstetrician. Her urine output during hospitalization ranged from 5–8 L/day. On examination, she was apparently in good health without definite evidence of dehydration, and her blood pressure was 110/80 mmHg and pulse rate was 114/minute. Laboratory results disclosed the following values: Total protein 6.9 g/dL, serum sodium 155 mmol/L, potassium 4.1 mmol/L, chloride 123 mmol/L, and serum and urine osmolality 316 mOsm/L and 138 mOsm/L, respectively, suggesting hemoconcentration. MR-CT imaging of the pituitary gland showed disappearance of a high intensity signal from the posterior lobe in a T1-weighted sequence, suggesting ADH depletion. A tentative diagnosis of central diabetes insipidus was made and the patient was given 1-desmino-8D-arginine-vasopressin (dDAVP), after which her urine output decreased significantly and serum and urine osmolality returned to normal ranges. She gave birth to a 3002 g male infant 5 weeks later. The labor was uneventful, however, water-deprivation and hypertonic saline challenge tests performed 2 and 3 weeks later, respectively, showed incomplete central diabetes insipidus. Following the birth, urine output decreased spontaneously and dDAVP was no longer needed, although MR-CT imaging of the pituitary gland showed that disappearance of the high intensity signal in the posterior lobe in a T1-weighted sequence persisted.

An association between pregnancy and diabetes insipidus is unusual, and most cases are transient. In the present patient, it was considered that pre-existing subclinical partial diabetes insipidus became unmasked by pregnancy, although the exact mechanism remains unclear.

Key words Polyuria, Polydipsia, ADH, Pregnancy

Introduction
Diabetes insipidus is a rare cause of urinary frequency during pregnancy, with estimated rates ranging from 2 to 4 of every 100,000 pregnancies.1 This condition has been tentatively classified as associated with pregnancy in patients with pre-existing diabetes insipidus, diabetes insipidus occurring during pregnancy, or diabetes insipidus occurring after delivery. Most of the cases belong to the second of those 3 conditions and are designated as transient diabetes insipidus during pregnancy (diabetes insipidus gravidarum). In the present report, we describe a patient with subclinical diabetes insipidus who developed transient central diabetes insipidus during pregnancy, along with a review of relevant literature.

Case Presentation
A 30-year-old woman was referred to our division because of polyuria and polydipsia. At the time of consultation, she was at 34 weeks of
gestation and being followed by an obstetrician. Her family history and past history were not remarkable, though she had experienced mild polyuria during the first pregnancy. On examination, she was apparently in good health with a regular pulse rate of 114 beats per minute, a respiratory rate of 19 per minute, and blood pressure of 110/80 mmHg. Her height was 146 cm and her weight was 52.5 kg. There were no other abnormal findings in her chest, abdomen, and extremities, however, her urine output ranged from 5–8 L/day during hospitalization. A laboratory examination disclosed the following values: Total protein 6.9 g/dL, serum sodium 158 mmol/L, potassium 4.1 mmol/L, chloride 123 mmol/L, calcium 9.1 mg/dL, and serum and urine osmolality of 316 mOsm/L and 138 mOsm/L, respectively, suggesting hemoconcentration. The results of a liver function test were AST 50 U/L, ALT 34 U/L, LDH 302 U/L, and Alp 448 U/L. The fasting plasma glucose level was 123 mg/dL and urinalysis findings were normal. At 35 weeks of gestation, the patient showed polyuria and her basal plasma ADH value was 0.59 pg/mL, despite high plasma osmolality (292 mOsm/L). Intravenous hydration was started, however, neither a water-deprivation test nor salt challenge test was performed during pregnancy. MR-CT imaging of the pituitary gland did not show swelling of the pituitary gland or thickening of the pituitary stalk, however, there was evidence of disappearance of a high intensity signal in the posterior lobe in a T1-weighted sequence, suggesting ADH depletion, although basal hormone secretion from the anterior pituitary gland was normal. A tentative diagnosis of central diabetes insipidus was made and she was given 1-desmino-8D-arginine-vasopressin (dDAVP) 2.5 µg twice intranasally, after which urine output decreased significantly and osmolality in serum and urine returned to normal ranges. At 39 weeks of gestation, the patient spontaneously gave birth to a 3,002 g male infant transvaginally and the labor was uneventful. Following the birth, urine volume decreased spontaneously and dDAVP was discontinued without recurrence of polyuria. An 8-hour water-deprivation test, according to the modified method of Miller-Moses, was performed 2 weeks after the delivery. After an overnight dehydration, an hourly urine collection was started, followed by 10 µg of intranasal dDAVP injection. After water deprivation, urine osmolality exceeded plasma osmolality, however, intranasal dDAVP administration increased urine osmolality by 17%. Thereafter, a hypertonic saline challenge test was performed 3 weeks after the delivery, during which 0.05 mL/kg/minute of 5% saline was infused for 2 hours. At the end of the test, plasma osmolality rose to 302 mOsm/L, however, ADH was only 2.66 pg/mL. These results are consistent with our earlier diagnosis of partial central diabetes mellitus. MR-CT imaging of the pituitary gland performed 4 months after delivery showed that the high intensity signal in the posterior lobe in a T1-weighted sequence remained absent (Fig. 1). Therefore, a final diagnosis of subclinical incomplete central diabetes insipidus unmasked by pregnancy was made.

**Discussion**

Polyuria/pollakiuria during pregnancy is often
associated with excessive thirst due to a reduction in the thirst threshold, hyperglycemia, urinary tract infection, or compression of the urinary bladder by the enlarged uterus. The occurrence of diabetes insipidus with pregnancy is considered to be rare, with the incidence estimated to be from 2 to 4 of every 100,000 pregnancies,¹ but comparable with the estimated prevalence of 1:25,000 in the general population.³ In the present patient, primary polydipsia was eliminated by the findings of increased serum osmolality and hypernatremia, while the response to intranasal dDAVP excluded nephrogenic diabetes insipidus. The present case was diagnosed with subclinical diabetes insipidus of the central type, which was not evident before pregnancy. During the previous pregnancy, she experienced similar symptoms, such as polyuria and polydipsia, thus, pregnancy might have been an aggravating factor for the development of overt central diabetes insipidus.

Although the causal linkage between diabetes insipidus and pregnancy remains unclear, several studies have speculated an underlying mechanism for this association.⁴⁻⁶ Possible explanations include: 1) increased glomerular filtration, 2) increased vasopressinase activity,⁷ 3) suppression of ADH secretion by swelling of the anterior lobe of the pituitary gland causing compression of the posterior lobe or by polydipsia due to a decreased thirst threshold,⁸ 4) increased hepatic and renal clearance of ADH,⁹ 5) hCG-induced reduction in osmotic threshold,¹⁰ and 6) resistance to ADH,⁹ possibly via increased renal prostaglandin production.¹¹,¹² In the present case, swelling of the pituitary gland was not observed, however, other factors such as increased vasopressinase activity, increased prostaglandin concentration, increased hepatic and renal clearance of ADH, hCG-induced reduction in osmotic threshold, and diminished reactivity of the renal tubules to ADH during pregnancy may have contributed to expose the pre-existing subclinical diabetes insipidus.

Transient diabetes insipidus during pregnancy can be divided into that associated with pregnancy and that associated with another pre-existing disease. The former shows increased vasopressinase activity due to reduced degradation as a result of impaired liver function,¹³ pre-eclampsia,¹⁴ or unknown etiology,⁷ thereby leading to transient diabetes insipidus, while the latter seems to be associated with a subclinical form of diabetes insipidus that becomes clinically evident only during pregnancy.¹,⁵,¹²,¹⁵,¹⁶ The MR-CT imaging and postpartum water deprivation and hypertonic saline challenge test findings, in which no polyuria was evident without dDAVP, indicated that the present case was subclinical diabetes insipidus of the central type, which was aggravated by pregnancy. In many patients with transient diabetes insipidus during pregnancy, MR-CT imaging and water deprivation testing is not performed after delivery, therefore the overall incidence of underlying subclinical diabetes insipidus may be underestimated.

For a diagnosis of diabetes insipidus during pregnancy, it is not recommended that a water-deprivation test be performed, since it will cause dehydration and hemoconcentration, leading to uteroplacental insufficiency that may be dangerous to both mother and fetus.¹⁵ However, dDAVP should be administered as early as possible when the condition is suggested, since it does not possess oxytocic or pressor activities, and will not lead to premature delivery.¹⁷ Moreover, since dDAVP does not appear in breast milk or possess teratogenic activity,¹⁸ it is safe to use during and after pregnancy.¹⁹ In conclusion, the findings in the present case indicate that pregnancy may unmask subclinical diabetes insipidus. Therefore, patients who develop polyuria and/or polydipsia during pregnancy should be tested during the postpartum stage to detect latent diabetes insipidus, as the results will provide invaluable information for early diagnosis and treatment for polyuria during a subsequent pregnancy, as cases of recurrent diabetes insipidus during pregnancy have been described.¹²,²⁰

References


