Polyuria and diabetes insipidus of pregnancy

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INTRODUCTION

Polyuria, a common complaint during normal pregnancy, is also one symptom of diabetes insipidus (DI). DI in pregnancy can be transient as a result of pregnancy-induced changes or represent worsening of preexisting central or nephrogenic DI. Recognition and management of DI during pregnancy is important because water restriction (as often occurs during labor and delivery) can result in serious neurologic consequences in both the mother and fetus.

This topic will discuss the clinical presentation, evaluation and diagnosis, and management of DI in pregnant patients. Related topics on polyuria and DI are presented separately:

- (See "Evaluation of patients with polyuria".)
- (See "Urine output in arginine vasopressin disorders (diabetes insipidus)".)
- (See "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Clinical manifestations and causes".)
- (See "Arginine vasopressin deficiency (central diabetes insipidus): Clinical manifestations and causes".)

DEFINITION

Polyuria is defined as abnormal urine output that exceeds 3 L per 24 hours [1]. By contrast, changes in the lower urinary tract function during pregnancy result in increased frequency of urination without increased urine output.

DI is a disorder characterized by polyuria and polydipsia that results from loss of urine concentrating ability of the kidneys. DI in pregnancy may be due to central (eg, head trauma,

pituitary adenoma) or nephrogenic (eg, gene mutations, lithium toxicity) causes, or a result of increased metabolic clearance of antidiuretic hormone (also known as gestational DI (table 1)) [2]. In all cases, the result is impaired renal water reabsorption, leading to production of a large volume of dilute urine. Urine osmolality and urine specific gravity are low. Both central and nephrogenic DI are discussed in detail elsewhere:

- (See "Arginine vasopressin deficiency (central diabetes insipidus): Clinical manifestations and causes".)
- (See "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Clinical manifestations and causes".)

EPIDEMIOLOGY

DI affects approximately 4 per 100,000 pregnancies [3]. The types of DI are presented in detail separately. (See "Evaluation of patients with polyuria", section on 'Causes of polyuria'.)

PATHOPHYSIOLOGY

Antidiuretic hormone and vasopressinase in pregnancy — Antidiuretic hormone (ADH) increases renal water reabsorption and decreases urine output. This effect is mediated by activation of the V2 receptor in the renal collecting tubules, resulting in enhanced renal water reabsorption and the formation of concentrated urine. Most DI is caused by either inadequate ADH production (central DI) or renal resistance to ADH (nephrogenic DI). (See "Urine output in arginine vasopressin disorders (diabetes insipidus)", section on 'Determinants of urine output'.)

Between the eighth gestational week and midpregnancy, the metabolic clearance of ADH increases four- to sixfold because of an increase in vasopressinase (also known as oxytocinase), which is produced by the placenta. Vasopressinase activity peaks in the third trimester, remains high during labor and delivery, and then falls to undetectable levels two to four weeks postpartum. In most pregnant patients, plasma concentrations of ADH remain in the normal range, despite increased metabolic clearance, because of a compensatory increase in ADH production by the pituitary gland. As a result, most patients do not become polyuric.

Transient diabetes insipidus of pregnancy — Transient DI of pregnancy is caused by an amplification of the normal pregnancy-related increase in vasopressinase levels or activity (table 1).

Patients with preeclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; and acute fatty liver of pregnancy are at increased risk for transient DI of

pregnancy. The mechanism in these cases is decreased degradation of vasopressinase due to hepatic dysfunction [4,5]. Patients with multiple gestations, because of a larger placental volume, have higher circulating levels of vasopressinase and thus are more likely to experience polyuria, particularly if there is coexistent hepatic dysfunction.

- (See "Preeclampsia: Clinical features and diagnosis", section on 'Oliguria'.)
- (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)
- (See "Acute fatty liver of pregnancy".)

Pregnancy-induced exacerbation of preexisting diabetes insipidus — Some pregnant patients have central or nephrogenic DI that was subclinical prior to pregnancy (table 1) [4,6,7]. On careful questioning, they typically describe polyuria and polydipsia prior to pregnancy, with worsening of symptoms during pregnancy. Placental vasopressinase, which degrades circulating endogenously secreted ADH (vasopressin), results in overt ADH deficiency in patients with preexisting partial, largely asymptomatic, DI. In these cases, polyuria tends to recur with every pregnancy. True ADH- and desmopressin-resistant nephrogenic DI has been reported in a few patients [6,8]. The mechanism is uncertain, but spontaneous resolution occurs after delivery.

- (See "Arginine vasopressin deficiency (central diabetes insipidus): Clinical manifestations and causes".)
- (See "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Clinical manifestations and causes".)

CLINICAL PRESENTATION

The typical presenting features of DI are polydipsia and polyuria; these symptoms can be difficult to distinguish from urinary frequency of normal pregnancy [2,4,6,9-14]. The possibility of central, nephrogenic, or transient DI should be considered in patients with intense polydipsia and polyuria, especially in the third trimester (table 1). Patients with DI generally report thirst and increased urinary output that are far greater than those normally seen in pregnant patients.

Hypernatremia does not occur unless access to water is restricted. In pregnant patients with DI who are undergoing cesarean birth or who are otherwise water restricted (eg, patients who are too ill to drink or with hyperemesis), severe hypernatremia can occur. The authors measure the serum sodium in any patient who reports polyuria and polydipsia, especially if access to water is limited. If serum sodium is >140 mEq/L, a diagnostic work-up for DI should be performed [2].

New-onset DI can also present acutely in the postpartum period when postpartum hemorrhage leads to pituitary hypoperfusion and infarction (ie, Sheehan syndrome) [6,15]. (See "Causes of hypopituitarism", section on 'Pituitary infarction (Sheehan syndrome)'.)

DIAGNOSTIC EVALUATION

A diagnostic evaluation for DI in pregnancy should be performed in patients with polyuria (urine output >3 L/day) or polydipsia, particularly if hypernatremia is present. A 24-hour urine collection should be done to confirm true polyuria, although collection can be cumbersome and is often incomplete (see "Evaluation of patients with polyuria"). DI of pregnancy (any cause) is diagnosed in pregnant patients with polyuria and polydipsia, an increased serum sodium (>140 mEq/L), and an inappropriately dilute urine (urine osmolality <300 mOsm/kg) [16].

Water restriction test — The standard confirmatory test for the diagnosis of DI is the water restriction test with assessment of urinary response to desmopressin. Desmopressin is not degraded by vasopressinase, so it is effective in increasing the urine osmolality and decreasing polyuria in patients with transient DI of pregnancy.

- For patients who are already hypernatremic (ie, serum sodium >143 mEq/L), the response to desmopressin (10 mcg intranasally or 4 mcg subcutaneously or intravenously) may be assessed without the need for further water restriction. (See "Evaluation of patients with polyuria", section on 'Patients with hypernatremia'.)

- For patients who have polyuria and polydipsia but normal serum sodium, water restriction is generally necessary. Water restriction must be completed in a hospital setting with close monitoring, as dehydration can result in uteroplacental insufficiency [12]. (See "Evaluation of patients with polyuria", section on 'Patients with a normal serum sodium'.)

Copeptin, a stable protein cosecreted with ADH, is emerging as a potential biomarker to distinguish central from nephrogenic DI in patients with polyuria/polydipsia. There are no data on use of this assay in pregnant patients for the evaluation of polyuria, though it has been studied as a predictor of preeclampsia [2,17].

DIFFERENTIAL DIAGNOSIS

When evaluating pregnant patients for possible DI, the clinician should consider and exclude the following:

- **Primary polydipsia –** Primary polydipsia, or psychogenic polydipsia, is a disorder of increased water intake, leading to increased urine output. In patients with primary polydipsia, limiting water intake results in a rapid reduction in polyuria and an increase in urine osmolality. Primary polydipsia does not cause hypernatremia. (See "Causes of hypotonic hyponatremia in adults", section on 'Primary polydipsia due to psychosis'.)

- **Urinary frequency without polyuria –** Urinary frequency is almost universal in pregnancy but does not usually reflect a pathologic increase in urine volume. Urinary frequency is distinguished from true polyuria by urine output less than 3 L/day in a 24-hour urine collection.

- **Hypernatremia due to inadequate water intake –** Hypernatremia (without polyuria) can develop in any individual with inadequate free water intake, such as a patient with hyperemesis gravidarum. This is easily distinguished from DI by the presence of an appropriately concentrated urine (urine osmolality >300 mOsm/kg, and usually much higher). In these cases, polyuria is absent and patients are often oliguric. Loop diuretics decrease urinary concentrating ability and must be held for this to be reliable.

MANAGEMENT

Management of DI in pregnancy includes treatment of hypernatremia (if present) and then treatment of the underlying cause.

- **Hypernatremia –** Hypernatremia in pregnancy, regardless of etiology, should be corrected by replacing free water. This may be done either orally or intravenously (ie, as 5% dextrose in water). Acute hypernatremia can be corrected rapidly. By contrast, chronic hypernatremia should be corrected slowly to reduce the risk of cerebral edema, a complication that has been reported primarily in infants. (See "Treatment of hypernatremia in adults", section on 'Choosing a rate of correction'.)

  In addition to correcting the free water deficit, ongoing free water losses from urine output and insensible losses should be replaced. An indwelling bladder catheter may be needed for accurate measurement of urine output if the patient is unable to cooperate with urine output measurement. (See "Treatment of hypernatremia in adults", section on 'Approach to therapy'.)

- **Transient or central DI –** Polyuria due to transient DI of pregnancy or central DI in pregnancy can be effectively treated with desmopressin (DDAVP), a vasopressin analog, which is resistant to degradation by vasopressinase [4,6,18]. For patients with intact thirst and access to water, a reasonable starting dose is 10 mcg intranasally or 0.05 mg orally, either at bedtime or twice daily. The dose should be titrated to achieve relief of

polyuria and a serum sodium of 133 to 140 mEq/L, targeting the mild physiologic hyponatremia of pregnancy [2,11]. Doses equal to or slightly higher than those used to treat central DI in nonpregnant patients are typically required [2]. The dose and dosing interval are adjusted to allow mild polyuria between doses and thus avoid severe hyponatremia. No adverse maternal or fetal effects from desmopressin use during pregnancy have been reported, although trial data are lacking [19]. Although DDAVP has a structure similar to oxytocin, use of intranasal DDAVP has not been associated with induction of labor [2]. (See "Arginine vasopressin deficiency (central diabetes insipidus): Treatment", section on 'Desmopressin'.)

- **Nephrogenic DI –** Management of polyuria in pregnant patients with nephrogenic DI in pregnancy can be difficult. Treatment strategies in nonpregnant patients include thiazide diuretics and nonsteroidal anti-inflammatory agents, but these agents are generally avoided in pregnancy. Similarly, a low-protein, low-sodium diet may decrease polyuria, but its safety in pregnancy has not been studied. Patients should be encouraged to drink to thirst, with continuous access to water, to avoid hypernatremia. (See "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Treatment".)

COMPLICATIONS

Hypernatremia can occur if water intake is restricted, as it often is in the peripartum period [11,13,20]. Pregnant patients with DI in whom oral intake must be restricted (eg, those undergoing cesarean birth) should be managed with hypotonic intravenous fluids at a rate to match their urine output and frequent monitoring of serum sodium concentration.

While the overall risk of obstetric complications is similar for patients with and without DI of pregnancy, limited data suggest an association between transient DI of pregnancy and preeclampsia [2,14,21,22]. Oligohydramnios has also been reported [20].

- (See "Preeclampsia: Clinical features and diagnosis".)
- (See "Preeclampsia: Antepartum management and timing of delivery".)
- (See "Oligohydramnios: Etiology, diagnosis, and management in singleton gestations".)

PROGNOSIS

Gestational DI caused by increased vasopressinase activity resolves postpartum and does not usually recur in subsequent pregnancies.

SUMMARY AND RECOMMENDATIONS

- Polyuria is defined as urine output that exceeds 3 L per 24 hours. Diabetes insipidus (DI) is a disorder characterized by polyuria and polydipsia that results from loss of urine concentrating ability of the kidneys. DI can result from central causes, nephrogenic causes, or be transiently related to pregnancy. DI occurs in approximately 4 per 100,000 pregnancies. (See 'Definition' above and 'Epidemiology' above.)

- Antidiuretic hormone (ADH) increases renal water reabsorption, thereby concentrating the urine. Between the eighth week and midpregnancy, the metabolic clearance of ADH increases four- to sixfold because of an increase in vasopressinase, which is produced by the placenta. (See 'Antidiuretic hormone and vasopressinase in pregnancy' above.)

- Transient DI of pregnancy is caused by an amplification of the normal pregnancy-related increase in vasopressinase levels or activity. Patients with preeclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; and acute fatty liver of pregnancy are at increased risk for transient DI of pregnancy, presumably through decreased degradation of vasopressinase in the setting of hepatic dysfunction. (See 'Transient diabetes insipidus of pregnancy' above.)

- Some pregnant patients with signs and symptoms of DI have central or nephrogenic DI that was subclinical prior to pregnancy. (See 'Pregnancy-induced exacerbation of preexisting diabetes insipidus' above.)

- The polydipsia and polyuria associated with DI in pregnancy can be difficult to distinguish from normal pregnancy. The possibility of central, nephrogenic, or transient DI should be considered in patients with intense polydipsia and polyuria (ie, more severe than typically seen in pregnancy) and in patients whose symptoms develop in the third trimester (table 1). (See 'Clinical presentation' above.)

- The diagnostic evaluation of DI in pregnancy begins with a 24-hour urine collection. Patients with polyuria, defined as a urine output that exceeds 3 L per 24 hours, require a desmopressin challenge with or without supervised water restriction. Some patients can delay evaluation until they are postpartum. (See 'Diagnostic evaluation' above.)

- The diagnosis of DI is confirmed in a patient with polyuria by an increased serum sodium (>140 mEq/L) and an inappropriately dilute urine (urine osmolality <300 mOsm/kg). (See 'Diagnostic evaluation' above and 'Water restriction test' above.)

- When evaluating pregnant patients for possible DI, the clinician should consider and exclude the following: primary polydipsia, urinary frequency (without polyuria), and hypernatremia due to inadequate water intake. (See 'Differential diagnosis' above.)

- Transient DI of pregnancy and central DI in pregnancy can be effectively treated with desmopressin (DDAVP), a vasopressin analog that is resistant to degradation by

vasopressinase. For patients with intact thirst and access to water, a reasonable starting dose is 10 mcg intranasally or 0.05 mg orally, either at bedtime or twice daily. (See 'Management' above.)

- Hypernatremia, which can occur if water intake is restricted, can result in serious neurologic consequences in both the mother and fetus. Hypernatremia should be treated with intravenous hypotonic fluid. (See 'Complications' above.)
- While the overall risk of obstetric complications is similar for patients with and without DI of pregnancy, limited data suggest an association between transient DI of pregnancy and preeclampsia. (See 'Complications' above.)
- Transient DI of pregnancy resolves postpartum and does not usually recur in subsequent pregnancies. (See 'Prognosis' above.)

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GRAPHICS

Comparison of types of diabetes insipidus in pregnancy

	Central DI in pregnancy	Nephrogenic DI in pregnancy	Transient DI of pregnancy
Associations	Sheehan syndrome (postpartum hypopituitarism), surgical trauma, head trauma, pituitary adenoma, autoimmune or other infiltration, idiopathic, *AVP* gene mutation, Wolfram syndrome, anorexia nervosa, toxin (alcohol, snake venom)	*AVPR2* and *Aquaporin-2* gene mutations, lithium toxicity, medullary cystic kidney disease, polycystic kidney, hypokalemia, hypercalcemia, sickle cell disease or trait	May be associated with preeclampsia and/or liver abnormalities. Can result in postpartum DI due to placental abruption resulting in release of vasopressinase.
Vasopressin sensitivity: Pathophysiology	Sensitive: Decreased secretory reserve of ADH from pituitary; ADH levels may be further decreased by clearance by placental vasopressinase	Resistant: Renal resistance to ADH	Sensitive: Increased placental vasopressinase mediated clearance of ADH
Timing of presentation	May present in any trimester, may be recurrent	May present in any trimester, may be recurrent	Typically presents in the third trimester, though symptoms may be as early as fourth week of gestation; rarely occurs postpartum (placental abruption)
Diagnosis: Response to DDAVP administration	Urine osmolality normalized	No change to urine osmolality	Urine osmolality normalized
Diagnosis: Plasma ADH level	Low to absent	Normal to high	Low to absent
Management	Responds to DDAVP	May be resistant to both ADH and DDAVP; consider hydrochlorothiazide or amiloride	Responds to DDAVP, resistant to ADH

DI: diabetes insipidus; ADH: antidiuretic hormone; DDAVP: desmopressin.

Graphic 115436 Version 2.0

Contributor Disclosures

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