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Diabetes insipidus and pregnancy

Diabète insipide et grossesse

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Abstract

Diabetes insipidus (DI) is a rare complication of pregnancy. It is usually transient, being due to increased placental production of vasopressinase that inactivates circulating vasopressin. Gestational, transient DI occurs late in pregnancy and disappears few days after delivery. Acquired central DI can also occur during pregnancy, for example in a patient with hypophysitis or neuroinfundibulitis during late pregnancy or postpartum. Finally, pre-existing central or nephrogenic DI may occasionally be unmasked by pregnancy. Treatment with dDAVP (desmopressin, Minirin®) is very effective on transient DI of pregnancy and also on pre-existing or acquired central DI. Contrary to vasopressin, dDAVP is not degraded by vasopressinase. Nephrogenic DI is insensitive to dDAVP and is therefore more difficult to treat during pregnancy if fluid intake needs to be restricted.

Keywords: Diabetes insipidus; Pregnancy; Arginine vasopressine; Vasopressinase; Placenta; Hypophysitis

Résumé

Le diabète insipide (DI) est une complication rare de la grossesse. Le plus souvent il s'agit d'un DI transitoire de la grossesse, en rapport avec une augmentation de la production, par le placenta, de vasopressinases qui inactivent la vasopressine circulante. Le DI gestationnel survient en fin de grossesse et disparaît en quelques jours après l'accouchement. Il peut s'agir également de DI centraux acquis pendant la grossesse, par exemple dans le cadre d'hypophysites ou de neuro-infundibulites de fin de grossesse ou au moment du postpartum. Plus rarement il s'agit de DI centraux ou néphrogéniques préexistant à la grossesse qui se démasquent pendant la grossesse. Le traitement par dDAVP (desmopressine, Minirin®) est très efficace en cas de DI transitoire de la grossesse ou de DI central acquis ou préexistant car les vasopressinases ne détruisent pas la dDAVP comme elles le font de la vasopressine. Les DI néphrogéniques, insensibles à la dDAVP, sont plus difficiles à traiter pendant la grossesse si l'accès à l'eau doit être limité.

Mots clés : Diabète insipide ; Grossesse ; Arginine vasopressine ; Vasopressinase ; Placenta ; Hypophysite

1. Introduction

Onset of diabetes insipidus (DI) during pregnancy is a very rare occurrence. The few available data suggest a prevalence of about 4 cases per 100,000 pregnancies [1]. The real figure is probably higher, however, as many cases are likely to go unnoticed, either because of the subclinical nature of DI, or because some obstetricians may overlook this diagnosis.

By definition, patients with DI eliminate large quantities (> 2–2.5 L per 24 hours, or 30 to 40 mL/kg of body weight) of hypotonic, hypo-osmolar urine (< 250–300 mOsm/kg H_2O) [2–6]. This is a non-osmotic polyuria, contrary to osmotic polyuria (solute excretion >60 mmol/h) where urine contains large amounts of osmotic substances, which may be either endogenous (urea, glucose. . .) or exogenous (glycerol, mannitol, radiological contrast media).

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2. Water homeostasis during pregnancy [7,8]

Water intake is regulated by thirst, which is controlled by specific hypothalamic centers sensitive to osmolality [9]. Water excretion by the kidneys is regulated by the antidiuretic hormone, arginine vasopressin (AVP). AVP is synthesized in the neurons located in the supraoptic and paraventricular hypothalamic nuclei, and migrates along axons, through the pituitary stalk, to the posterior pituitary, where it is stored [3]. During its transport along axons, AVP is also matured. AVP is released by exocytosis in response to increased plasma osmolality. It is then transported by the circulation to the kidney, at the level of collecting duct where it activates AVP receptors (V2 receptors). These seven-transmembrane-domains receptors are coupled to adenylate cyclase and to cAMP production, and allow water reabsorption by mobilizing aquaporin 2 [3,10].

During normal pregnancy, human chorionic gonadotropin (hCG) lowers the plasma osmolality threshold at which AVP release and thirst are triggered [11–13]. This contributes to reductions in natremia (by about 5 mmol/L) and plasma osmolality (by about 10 mOsmol/kg) [13,14].

The placenta plays another important role in water homeostasis during pregnancy by producing vasopressinase (a trophoblast-derived aminopeptidase), which inactivates endogenous vasopressin [15]. Vasopressinase is produced as early as the seventh week of gestation, reaching its maximum concentration during the third trimester [15–18]. At 22–24 weeks of pregnancy, vasopressin degradation reaches a plateau that persists until delivery, resulting in a compensatory increase in AVP synthesis and secretion [17,19].

Serum vasopressinase activity correlates with placental weight and is higher during multiple pregnancies [20].

Placenta-derived vasopressinase concentrations collapse after delivery.

3. Diagnosis of DI in a pregnant woman with hypotonic polyuria

Investigation of a polyurodipsic state during pregnancy must first establish that it is secondary to hypotonic polyuria and not to osmotic polyuria (by checking glycosuria, for example). Indeed, urine osmolarity is low in this setting (< 300 mOsm/L), contrasting with high plasma osmolality (> 280 mOsm/L) and with rather high serum sodium levels (often > 140 mmol/L), which, in the context of pregnancy, is unusual (natremia is usually in the lower range of normal during pregnancy).

If hypotonic polyuria is confirmed, then primary polydipsia, which is often accompanied by potomania, can be rapidly ruled out in the absence of psychiatric disorders, and a diagnosis of authentic DI can be made. AVP assay is not contributory, and copeptin assay has not been reported in this context of central DI [6,21]. A water deprivation test is contraindicated during pregnancy because of the risk of hypernatremia, neurological disorders, and fetal harm.

Transient DI of pregnancy is confirmed by the therapeutic efficacy of dDAVP, which increases urine osmolarity and reduces diuresis (vasopressinase does not inactivate dDAVP) and by the fact that dDAVP can safely be withdrawn in the postpartum, which is not the case in patients with pre-existing central DI.

Nephrogenic DI is accompanied by high AVP or copeptin concentrations.

The possibility of DI (whatever its etiology) should also be raised in case of unexplained polyhydramnios [22,23].

4. Etiologic diagnosis of DI during pregnancy

4.1. Transient DI of pregnancy

Transient DI of pregnancy, or gestational DI, usually occurs during the third trimester. It is the most common form of DI during pregnancy [7,24] and is therefore the first diagnosis to be considered.

Transient diabetes insipidus of pregnancy is associated with an increased vasopressinase concentration [25,26], secondary to an increase in placental production, in case of multiple pregnancies for example, or impaired hepatic vasopressinase degradation due to pre-eclampsia, eclampsia or the HELLP syndrome [24,27–32].

Vasopressinase activity usually declines after delivery and becomes undetectable within 5–6 weeks postpartum [33].

Cases of isolated DI occurring not at the end of pregnancy but in the immediate postpartum have also been described, again related to an increase in vasopressinase activity [33]. This situation must be distinguished from DI associated with Sheehan's syndrome or with lymphocytic hypophysitis, which is also more frequent in the postpartum; these forms are often associated with other pituitary disorders and persist for after delivery. In a recent study of HEK293 cells transfected with the AVP V2 receptor coupled to luciferase, the serum of a patient with transient DI was unable to activate luciferase, contrary to normal serum or stimulation with AVP or dDAVP, which produce a ~ 50-fold increase [33]. A few days after delivery, once the polyurodipsic syndrome had disappeared, the patient's serum recovered its ability to stimulate luciferase activity, confirming the disappearance of vasopressinase [32].

Symptoms resolve spontaneously and the response to fluid restriction normalizes in the weeks following delivery, further confirming the diagnosis of transient DI of pregnancy [30]. Transient DI does not usually recur during subsequent pregnancies.

4.2. Central DI during pregnancy

During normal pregnancy, AVP release increases to maintain water reabsorption and thus to prevent polyuria. However, when AVP secretion is impaired, either because of DI onset (due to neuroinfundibulitis of pregnancy for example) or because of pre-existing subclinical DI (central or nephrogenic), the pregnancy can unmask polyuria and polydipsia [34].

Common causes of central DI include tumors, pituitary infiltrations, sequelae of infundibulitis, and genetic abnormalities [6].