Gestational Diabetes Insipidus: A Review of an Underdiagnosed Condition

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Abstract

Objective: To review the etiology, diagnosis, and management of diabetes insipidus during pregnancy.

Data Sources: A search of the literature was performed in PubMed using key word searching and citation snowballing to identify articles published in English between January 1, 1980, and December 31, 2008, on the subject of diabetes insipidus during pregnancy. Once the articles were identified, a thorough review of all results was conducted. Results and conclusions were compiled and summarized.

Study Selection: We reviewed 50 studies selected using the following key words: diabetes insipidus, pregnancy, arginine vasopressin, vasopressinase.

Conclusion: Gestational diabetes insipidus is underdiagnosed because polyuria is often considered normal during pregnancy. Clinicians caring for pregnant women should consider screening for gestational diabetes insipidus, because it could be associated with serious underlying pathology.

Résumé

Objectif : Analyser l'étiologie, le diagnostic et la prise en charge du diabète insipide pendant la grossesse.

Sources de données : Des recherches ont été menées dans PubMed en vue d'en tirer les articles publiés en anglais, entre le 1er janvier 1980 et le 31 décembre 2008, qui traitaient du diabète insipide pendant la grossesse, et ce, au moyen de mots clés et à partir des citations se trouvant au sein des articles identifiés. Une fois ces articles identifiés, une analyse exhaustive de tous les résultats a été menée. Les résultats et les conclusions ont été compilés et résumés.

Sélection d'étude : Nous avons analysé 50 études sélectionnées au moyen des mots clés suivants : *diabetes insipidus*, *pregnancy*, *arginine vasopressin*, *vasopressinase*.

Conclusion : Le diabète insipide gestationnel est sous-diagnostiqué en raison du fait que la polyurie est souvent considérée normale pendant la grossesse. Les cliniciens qui assurent la prise en charge des femmes enceintes devraient envisager le dépistage du diabète insipide gestationnel, puisque celui-ci pourrait être associé à une grave pathologie sous-jacente.

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Key Words: Diabetes insipidus, pregnancy, arginine vasopressin, vasopressinase

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INTRODUCTION

Diabetes insipidus during pregnancy is a rare phenomenon whose incidence is estimated at between two and six cases per 100 000 pregnancies.[1] It was identified more than 200 years ago with a standard clinical profile.[2,3] It can occur at any stage of gestation, but it generally occurs at the end of the second or during the third trimester of a first pregnancy and sometimes after delivery. Few cases have been reported over the last 30 years.

Clinical Features

DI has a rapidly progressive onset. It is characterized by the appearance of a polyuric-polydipsic syndrome that results in fluid intake ranging from 3 to 20 L/day.[4] It is also characterized by excretion of abnormally high volumes of diluted urine. This polyuria is insipid, i.e., the urine concentration of dissolved substances is very low.[4] Because of a decrease in the ability to concentrate urine, introduced liquids are not adequately reabsorbed by the renal collecting system. When urine is collected while the patient drinks ad libitum, urine volume over 24 hours can exceed 50 mL/kg body weight, whereas urinary density and osmolality are lower than

1.010 g/mL and 300 mOsm/kg of water consumed, respectively.[5,6] Nocturnal polyuria can be the principal reason for consultation with a physician.

Polyuria is generally associated with intense thirst and a large increase in fluid intake (polydipsia), leading to increased urinary secretion.[4] Symptoms of DI are benign and usually well tolerated when the sensation of thirst is not altered. Patients often neglect these symptoms, thinking they are symptoms of the pregnancy. Indeed, if the patient takes in a sufficient quantity of liquids, she is not aware of the acute episodes of dehydration.

Etiology

DI can be the result of several factors. The most frequent cause is a deficit in the secretion of hypothalamo-hypophyseal ADH, and this usually results in neurogenic or central DI. The second cause of DI, renal tubular insensitivity to ADH resulting in nephrogenic or peripheral DI, is less common.[4,6,7] The third cause is again the result of a deficit in ADH production, but in this case the deficit is secondary to excessive fluid intake.[6] An anomalous thirst or a psychosis such as psychogenic polydipsia can thus induce psychogenic DI. During pregnancy an abnormal increase in clearance of the hormone may cause the ADH deficiency and provoke gestational DI.[6]

PHYSIOLOGICAL MODIFICATIONS IN THE METABOLISM OF WATER DURING PREGNANCY

Background

Extracellular osmolality is controlled by the mechanism of thirst and the secretion of the ADH vasopressin.[8] An increase in plasma osmolality stimulates the release of ADH by the posterior pituitary and causes the perception of thirst in order to stimulate fluid intake to decrease POsm. The physiological mechanisms of this osmoregulation are modified during pregnancy.

The osmotic threshold of the perception of thirst falls after the fifth week of amenorrhea.[9,10] The patient thus feels thirst with a lower POsm (10 mOsm/kg below POsm in the non-pregnant state). Chorionic gonadotropin seems to be responsible for modifications in the osmotic threshold; if non-pregnant women are injected with 10 000 IU of hCG intramuscularly per day for five days, their POsm and their osmotic thresholds decrease.[11] Moreover, molar pregnancy (in which there is a significant excess of circulating hCG) is associated with a decrease in the osmotic thresholds for perception of thirst and secretion of ADH. Davison et al. showed in 1988 that evacuation of a molar pregnancy resulted in a progressive normalization of the thresholds, which correlated with the fall in plasma concentrations of hCG.[11] This decrease in the osmotic threshold of the perception of thirst results in dilution of body fluids.[9]

Pregnancy-associated hemodilution can be detected as early as the sixth week of amenorrhea. Compared with values in non-pregnant women, there is a physiological decrease in POsm (by 10mOsmol/L) and sodium concentration (by approximately 4 mmol/L).[11] This observed decrease in osmolality seems to be maintained by a lowering of the ADH secretion threshold. This decrease corresponds closely to the decrease in the osmotic threshold of perception of thirst. The ADH secretion threshold is thus reduced by 6 mOsmol/kg. The secretion of ADH, which is usually inhibited when POsm reaches 285 mOsmol/L, persists in the patient, resulting in fluid retention, a decrease in POsm, and an increase in blood volume.[11] Reactivity to ADH is maintained but with simultaneously lower osmotic thresholds in ADH secretion and perception of thirst. This is why plasma levels of ADH are the same before and during pregnancy, despite a physiological increase in ADH clearance.

The metabolic clearance of ADH increases four- to six-fold between the eighth week of pregnancy and the middle of pregnancy.[12] The syncytiotrophoblast of the human placenta is known to play an important role in the production of vasopressinase (a cystine amino-terminal peptidase), which quickly degrades ADH and oxytocin in vivo and in vitro.[13] In the pregnant ewe, the placenta does not produce vasopressinase, and an increase in ADH metabolism is not seen.[14] Clearance of desamino-D arginine vasopressin (1-desamino-8-D-arginine vasopressin), which is not inactivated by vasopressinase, is barely increased during the third trimester of pregnancy.[15] It is currently accepted that placental vasopressinase is responsible for the increase in ADH clearance during pregnancy. The evidence suggests levels of vasopressinase increase 1000-fold during pregnancy.

The activity of this enzyme increases gradually during pregnancy and reaches its peak during the third trimester. Activity remains high during labour and delivery and then decreases by 25% per day to become undetectable between postpartum weeks two and four.[13] This activity is

ABBREVIATIONS

ADH	antidiuretic hormone
DDAVP	desamino-D arginine vasopressin (1-desamino-8-D-arginine vasopressin)
DI	diabetes insipidus
GDI	gestational diabetes insipidus
hCG	human chorionic gonadotropin
HELLP	hemolysis, elevated liver enzymes, and low platelets
PGE_2	prostaglandin E_2 (dinoprostone)
POsm	plasma osmalality

Classification of GDI

Clinical context	Pathophysiology	Progression
1. Pre-existing DI		
1.1 Exacerbated nephrogenic DI	Decrease in osmotic thirst threshold	Recurrence at next pregnancy
	Increase in hydrous contributions resulting in increased renal resistance to ADH	Extremely rare
1.2 Sub-clinical ADH deficit	Decrease in osmotic thirst threshold	Recurrence at next pregnancy
	Increase in ADH clearance related to pregnancy cannot be compensated by an increase in ADH secretion	
2. Transient DI During Pregnancy		
Hepatic disturbance	Decrease in hepatic clearance of vasopressinase	Cured with standardization of hepatic function
Acute fatty liver		
Preeclampsia	Increase in ADH degradation	Recurrence if hepatic disturbance at next pregnancy
HELLP		
Idiopathic		
3. DI After Delivery		
Permanent hypopituitarism		Permanent DI
Sheehan's syndrome	Pituitary infarction during peripartum	Permanent DI
Autoimmune hypophysitis	Pituitary failure	Transient DI

particularly increased during multiple pregnancies.[16] It is believed that vasopressinase is metabolized in the liver.

The phenomenon of urinary concentration is maintained in pregnant women by a lowering of the threshold for ADH secretion, resulting in increased production of ADH to maintain homeostasis. Indeed, despite these changes, the plasma concentration of ADH is equal to that seen in the non-pregnant state (1–2 pg/mL). Thus, there is an increase in ADH secretion, which compensates for its increased degradation.

Pathogenesis

Several physiological mechanisms contribute to the occurrence of gestational DI in patients who have either a reduced capacity to secrete ADH or an altered action of ADH.

The first of these, a decrease in capacity to secrete vasopressin, is related to a physiological increase in the activity of vasopressinase.[17] The second reflects an increase in the concentrations of corticosteroids, progesterone, and thyroxin, which antagonize ADH.[18]

An increased production of renal prostaglandins (especially PGE_2) during pregnancy can reduce renal sensitivity to ADH at the level of the renal tubules, resulting in an increase in polyuria in patients with partial DI of nephrogenic etiology.[19] Production of prostaglandins can be blocked by administration of 1 to 2 g ASA without affecting osmolality levels or urinary volumes. The patient thus maintains a lower POsm within narrow limits.

CLASSIFICATION OF GESTATIONAL DIABETES INSIPIDUS

Patients with GDI can be classified into three independent groups (Table).[17]

1. Pre-existing DI

In the majority of cases (group 1), subclinical DI seems to have been present prior to pregnancy. These patients may present with latent DI that is due to production of placental vasopressinase, which degrades circulating endogenous vasopressin. The deficit in ADH is thus secondary to an increased capacity to clear the hormone. Pregnancy worsens the condition because of a deficiency in the ADH-secreting ability of the post-pituitary gland. Indeed, and to varying degrees, these patients have pre-existing deficits in vasopressin and reduced ADH-secreting reserves, and are thus unable to maintain hydrous homeostasis when confronted with the physiological challenge of compensating for the increase in ADH clearance.[20]

Subclinical DI generally appears in the third trimester or earlier if the ADH deficit is significant. Pre-existing subclinical DI occurs more frequently than nephrogenic DI that is due to a deficiency in ADH secretion (post-trauma following previous hypophyseal surgery or idiopathic).

Soule et al.[21] described a 23-year-old female patient who underwent transphenoidal surgery for a hypophyseal microadenoma. During the five years following surgery, this patient was treated with DDAVP, which was discontinued when she learned to manage her polyuria. Thirteen years later during an induced pregnancy, she developed polyuria (5 L/day) associated with polydipsia at 36 weeks' gestation. A water deprivation test confirmed the diagnosis of GDI. Resumption of treatment (DDAVP 10 μg twice daily) resulted in a reduction in diuresis from 300 to 400 mL per hour to 50 mL per hour. The GDI resolved two weeks after delivery, and treatment with DDAVP was discontinued because of this.[21]

Subclinical DI seems to occur more frequently in multiple pregnancies.[16] A larger placental volume may correlate with increased secretion of vasopressinase. Subclinical DI may also be the first clinical indicator of tumours located in the hypothalamic-pituitary area. Further, during pregnancy an increase in the size of craniopharyngiomas and prolactinomas is often seen, potentially compressing the post-pituitary gland. Latent DI frequently worsens during pregnancy. Moreover, urinary volume stabilizes corresponding to decreases in tumour size.[22]

During the treatment of pre-existing DI, the amount of DDAVP must be increased accordingly. Most cases of latent DI respond well to low doses of DDAVP, resulting in no deterioration in hepatic function and normal increases in placental production of vasopressinase. After delivery of the placenta, normal ADH metabolism and normal diuresis returns in two to three weeks. In these patients, recurrences are expected during subsequent pregnancies.

2. Transient DI During Pregnancy

The second group consists of patients with GDI with an abnormal increase in vasopressinase activity. This increase is frequently associated with preeclampsia and anomalies of hepatic function. Patients in this group have a disturbance in hepatic function that can occur in preeclampsia,[23] HELLP syndrome,[7,24] acute fatty liver,[25] or an idiopathic condition.[12] The hypothetical cause is hepatic dysfunction that reduces vasopressinase degradation, significantly increasing circulating concentrations of vasopressinase and consequently increasing clearance of vasopressin, eventually resulting in DI.

Preeclampsia is accompanied by a decrease in hepatic function that could contribute to increased vasopressinase activity by a decrease in its degradation. Cammu et al.[26] described six cases of transitory DI associated with hepatitis. Histological examination in one case revealed non-specific acute hepatitis without steatosis, similar to that observed in HELLP. The cause of the hepatitis was not known, but it often occurs at end of pregnancy.[26]

In some cases HELLP syndrome is accompanied by GDI.[24,27–31] In three reported cases (one multiple pregnancy and two singletons), a combination of HELLP and GDI was detected between weeks 35 and 37 of pregnancy. This suggests that the most probable mechanism responsible for the appearance of GDI in these cases is increased placental volume related to increased vasopressinase production. In another report (a singleton pregnancy), the combination of HELLP and GDI occurred at week 16.[24] The most probable cause of transient DI is reduced vasopressinase degradation due to liver damage. This is the mechanism most often responsible for the development of transient DI in three other reported cases in multiple pregnancies, in which this syndrome developed during the postpartum period.[27,30,31]

Vasopressinase degrades vasopressin by withdrawing amino acids from its N-terminal portion; the C-terminal segment exhibits hypertensive properties.[32] Thus, an increase in vasopressinase activity may increase the quantity of degraded vasopressin while having no effect on the C-terminal portion, which would explain the high rate of preeclampsia in patients developing DI during pregnancy. According to Hamai et al.,[33] pregnancies in which DI develops are often characterized by symptoms of preeclampsia, but this is not the case when DI was present before pregnancy.

It is necessary to monitor patients developing GDI closely because the risks of preeclampsia and deterioration of hepatic function are significant. Conversely, at the onset of preeclampsia, possible onset of GDI should be considered when urinary volume increases.[34] In these patients, DI can be controlled by the administration of DDAVP, which has an effective antidiuretic action without risk of hypertension. This situation resolves with normalization of hepatic function. The onset of GDI is generally benign and quickly reversible after delivery. It will not recur during later pregnancies unless hepatic pathology reappears.

3. DI After Delivery

DI rarely occurs postpartum. It can be transient in the presence of temporary hepatic insufficiency or when accompanied by postpartum autoimmune hypophysitis.[35] It can also be permanent if accompanied by permanent hypopituitarism. Sheehan's syndrome (partial or total necrosis of the anterior pituitary gland secondary to hemorrhagic shock or significant bleeding) is characterized by an insufficiency of the anterior pituitary gland.[36,37] When necrosis extends to the posterior lobe, DI can occur. A concomitant attack on the supraoptic neurons could result in

DI, suggesting a hypothalamic rather than hypophyseal origin.

In patients with a pituitary tumour, hemorrhage within the tumour can occur postpartum. Pituitary apoplexy occurring during pregnancy is rare. Several authors identified a correlation between tumour size and the risk of pituitary apoplexy.[38] Increased estrogenic activity during pregnancy results in an increase in the size of the pituitary gland and of pituitary tumours. Thus, it is not surprising that hemorrhagic risk is significant in these patients.[39]

DIAGNOSIS OF DI DURING PREGNANCY

Clinical Examination

The clinical examination is normal when the GDI patient is drinking ad libitum. There are no signs of dehydration or orthostatic hypotension if there is no restriction of the water intake. On the other hand, disturbances in hydration can occur in obtunded or comatose patients because of the absence of compensation for urinary fluid losses, mainly because thirst is neither felt nor satisfied. Bitemporal visual field deficits related to pituitary abnormalities may be present. To isolate various causes of GDI, it is important to consider any history of neurosurgical interventions or psychological difficulties. Patients with preeclampsia have a disturbance in hepatic function, which could result in increases in vasopressinase activity and GDI respectively; hence, blood-pressure measurements should be performed.

Investigations

Laboratory results are usually normal in patients with GDI, but the clinician must consider that during pregnancy POsm decreases by almost 10 mmol/L[40] and sodium concentration decreases by almost 5 mEq/L.[9] Urinary osmolality will be significantly reduced; nevertheless, fluid intake, urine output, plasma concentration of ADH, POsm, and levels of sodium and glucose in blood and urine should be assessed in patients who have signs and symptoms suggestive of GDI. Measurement of hepatic transaminases, serum creatinine and uric acid should also be performed in these patients.

Polyuria caused by GDI is distinguished from polyuria in poorly controlled diabetes mellitus by the absence of glucose in urine. Blood glucose levels are usually normal in GDI, but a case of diabetes mellitus associated with GDI was described by Grimaldi et al.[41] GDI can also be suspected when blood osmolality is comparable with that of a non-pregnant woman (> 285 mOsmol/L) with urinary osmolality under 300 mOsmol/L. The blood of pregnant women contains high concentrations of cystine aminopeptidase, which is able to degrade vasopressin in vitro. This is why plasma levels of ADH should be assayed in the presence of a vasopressinase inhibitor.[9] Vasopressinase activity levels can be obtained by chromatography.

The essential differential diagnosis is psychogenic polydipsia. In this psychosis, the sensation of thirst is abnormally increased and induces a secondary polyuria (due to so-called primary polydipsia). It is the opposite of GDI, in which polyuria is primary and polydipsia is secondary. Psychogenic polydipsia can be distinguished from GDI by a water deprivation test. This test must be carried out in a hospital setting under close monitoring and should be undertaken with caution during pregnancy because dehydration can induce uteroplacental insufficiency due to decreased plasma volume. In patients with psychogenic polydipsia, the decrease in fluid intake results in cessation of polyuria. Since the test is poorly tolerated in patients with GDI, it should be quickly terminated if there is no obvious reduction in polyuria.

If a diagnosis of acute fatty liver is suspected, clinical and biochemical findings and an ultrasound examination or computed tomography should be correlated with serological markers for viral hepatitis.[42]

To differentiate between vasopressin-responsive and vasopressin-resistant forms of GDI, vasopressin is administered intramuscularly and urine osmolality monitored.[1]

Cerebral MRI

During normal pregnancy, there is an increase in the size of the anterior pituitary due to hyperplasia and hypertrophy of the lactotroph cells. The posterior pituitary decreases in volume during the early stages of pregnancy and is generally not visible on imaging by the end of pregnancy because it is pushed posteriorly by the anterior pituitary. A normal posterior pituitary gland is found in 90% of subjects as a spontaneous hypersignal in T1, which represents the functions of storage and release of ADH in all women. In patients with GDI, there is a loss of the hypersignal in the posterior pituitary gland because of a decrease in vasopressin reserves.[43]

Cerebral MRI can also identify a pituitary tumour.[44]

Obstetrical Ultrasonography

Obstetrical ultrasonography, with close monitoring of fetal growth and Doppler imaging of uterine arteries, is justified in women with GDI because of the frequent association of GDI with preeclampsia. Measurement of the amniotic fluid index can be carried out to identify oligohydramnios that may occur during GDI.[44]

TREATMENT

Administration of intranasal DDAVP is the treatment of choice in GDI.[1] Unlike natural vasopressin, DDAVP, a synthetic analogue of vasopressin, resists degradation by vasopressinase.[45] Doses of DDAVP must be equal to or slightly higher than the doses recommended for central DI diagnosed in the non-pregnant state.

Treatment begins with nasal instillation of DDAVP in the evening. It is preferable to aim for a diuresis of 2 to 3 litres per 24 hours, rather than to risk a DDAVP overdose that could easily lead to hyponatremia.

According to Kallen and colleagues,[46] exposure to DDAVP during pregnancy does not increase the risk of fetal malformation, even when exposure occurs over the entire pregnancy. However, other reports describe cases where five of six mothers treated with DDAVP during pregnancy had placental insufficiency resulting in dystrophic children.[47,48]

Breastfeeding can stimulate secretion of ADH by nonosmotic mechanisms, in which case the dose of administered DDAVP can be decreased. The potential role of oxytocin remains to be explored. DDAVP is secreted in mother's milk in very small quantities. Moreover, it is only minimally absorbed by the digestive tract of the child and poses little risk for the development of fluid and electrolyte disorders.

DDAVP is also preferable for use in women with preeclampsia because of its limited effect on vascular tone. Recent reports suggest that the quantity of amniotic fluid may change during DDAVP administration.[44,49]

The second line of treatment in patients with GDI is hydrochlorothiazide.[50] Potential complications of hydrochlorothiazide are fetal hypoglycemia and neonatal DI. Treatment must be discontinued after remission of DI, which occurs two to three weeks after delivery.

CONCLUSION

The diagnosis of gestational DI is often not considered during pregnancy because polyuria in pregnancy is generally considered normal. GDI does not seem to result in serious complications over the course of the pregnancy. Certain forms, however, can be associated with serious pathology and should be screened for. Clinicians caring for pregnant women need to be aware of the challenges related to the secretion and normal action of antidiuretic hormones during pregnancy.

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