Gestational Diabetes Insipidus: A Review of an Underdiagnosed Condition

Nikolay Aleksandrov, MD,[1] François Audibert, MD, MSc,[1,2] Marie-Josée Bedard, MD, FRCSC,[1,3] Michèle Mahone, MD, FRCPC,[3,4] François Goffinet, MD, PhD,[5,6] Isaac-Jacques Kadoch, MD[1,3]

[1]Department of Obstetrics and Gynecology, University of Montreal, Montreal QC

[2]Sainte Justine Hospital, Montreal QC

[3]Centre Hospitalier Universitaire de Montréal, Hôpital Saint-Luc du CHUM, Montreal QC

[4]Department of Internal Medicine, University of Montreal, Montreal QC

[5]INSERM Epidemiological Research Unit on Perinatal Health and Women's Health, Université Pierre et Marie Curie Paris VI, Paris, France

[6]Faculté de médecine, Maternité de Port-Royal, Hôpital Cochin Saint-Vincent-de-Paul, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France

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.

J Obstet Gynaecol Can 2010;32(3):225–231

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

Competing Interests: None declared.

Received on March 17, 2009

Accepted on July 13, 2009

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