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Diabetes insipidus during pregnancy

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Diabetes insipidus (DI) in pregnancy is a heterogeneous syndrome, most classically presenting with polyuria and polydipsia that can complicate approximately 1 in 30,000 pregnancies. The presentation can involve exacerbation of central or nephrogenic DI during pregnancy, which may have been either overt or subclinical prior to pregnancy. Women without preexisting DI can also be affected by the actions of placental vasopressinase which increases in activity between the 4th and 38th weeks of gestation, leading to accelerated metabolism of AVP and causing a transient form of DI of pregnancy. This type of DI may be associated with certain complications during pregnancy and delivery, such as pre-eclampsia. Management of DI of pregnancy depends on the pathophysiology of the disease; forms of DI that lack AVP can be treated with desmopressin (DDAVP), while forms of DI that involve resistance to AVP require evaluation of the underlying causes.

Introduction

Diabetes insipidus is part of a spectrum of disorders that presents with polyuria and polydipsia and is related to insufficient secretion of or impaired renal response to vasopressin (AVP, anti-diuretic hormone/ADH). This condition can also present during pregnancy, due to normal human gestation causing a variety of effects on the maternal hypothalamic-pituitary axis and the metabolism of AVP. Diabetes insipidus was first reported in pregnancy in 1942, and has subsequently been shown to complicate at least 4 out of 100,000 cases of pregnancy [1,2]. Because of changes to maternal volume status and hemodynamics, as well as osmotic homeostasis, it is important for health care providers to

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quickly identify, evaluate and manage DI during pregnancy. This review focuses on a brief overview of vasopressin physiology and its relevance to pregnancy followed by a review of the clinical presentation of DI during pregnancy, including the pathophysiology, epidemiology and management of the several of subtypes of DI in pregnancy.

Vasopressin (AVP) physiology

Vasopressin (AVP, i.e., anti-diuretic hormone/ADH), is synthesized in a circadian manner in the neurosecretory magno-cellular neurons of the lateral and superior regions of the paraventricular nuclei and the supraoptic nuclei of the hypothalamus [3]. As the synthesized prohormone is transported down the neurohypophyseal axons in neurosecretory vesicles, it is cleaved to produce AVP on its way to storage in the posterior pituitary [4]. This entire process takes 1–2 h from synthesis to storage [5].

Nearby but distinct nuclei within these regions of the hypothalamus produce oxytocin, the other hormone secreted by the posterior pituitary. Oxytocin regulates smooth muscle contractions during gestation, leading to both uterine contractions as well as milk-let-down post partum [6]. Following synthesis of AVP and oxytocin in the cell bodies of the hypothalamus, the hormone-containing secretory granules migrate from the hypothalamus down the supraopticohypophyseal tract into the posterior pituitary, where these hormones are stored prior to release into the systemic circulation.

AVP release from the posterior pituitary via exocytosis is stimulated by increased plasma osmolality (based on signaling from osmoreceptors of the anterior pituitary), decreased circulating volume, nausea, vomiting, stress, hypoxia and exercise [7]. Its release is inhibited by reduced plasma osmolality, increased plasma volume and substances such as alcohol and opiates [8]. Plasma osmolality is tightly regulated and there is a threshold plasma osmolality level above which AVP is released in proportion to increases in plasma osmolality. A change as small as a 1% increase in osmolality above 280 mOsm/kg will cause the osmoreceptors to signal AVP release [9]. Thirst is stimulated at an equivalent or slightly higher plasma osmolality.

AVP is released from the posterior pituitary, and its effects are mediated via 4 different G-protein coupled receptors. The V1a receptor's most well-defined roles include activating vasoconstriction, gluconeogenesis, platelet aggregation, hypothermia and appetite [5,4]. The V1b receptor primarily potentiates the action of corticotrophin releasing hormone, releasing ACTH from the anterior pituitary [10]. The majority of AVP's osmotic regulatory effects occur via activation of the V2 receptors located primarily in the distal convoluted tubules, the collecting ducts of the kidney and the vascular endothelium. This receptor signals the insertion of previously formed aquaporin-2 channels into the apical membrane of renal tubular cells to stimulate water absorption, thus maintaining plasma volume and urine osmolality [11].

With relevance to pregnancy, AVP also has affinity to the oxytocin receptor at a similar affinity compared to oxytocin though the converse does not prove true, with oxytocin having a 30-fold lower affinity to the V1a receptor compared with AVP itself [12]. AVP, with a half-life of 10–35 min, is eventually metabolized by endogenous vasopressinases in the kidneys and liver [13].

Pregnancy related changes in osmotic homeostasis

Major changes occur in the pituitary gland during pregnancy, altering the anatomy and physiology of the gland. The posterior pituitary specifically is affected by the resetting, namely reduction, of the set point of the osmoregulatory system during pregnancy [14,15]. As a result, AVP is released at a lower concentration.

Maternal physiology is altered as well, with shifts in maternal blood volume in addition to osmoregulation. A further contributing factor is the thirst mechanism, which changes during pregnancy resulting in a reduced threshold for thirst, with more thirst at a lower serum osmolality and serum sodium compared to the non-pregnant state. These effects may be mediated by an effect of human chorionic gonadotropin (HCG) [16–18]. Maternal urine output may be increased due to an increased glomerular filtration rate and increased renal prostaglandin E2 during pregnancy. Clinically, this results in increased polydipsia and polyuria, with increased water retention, a decreased plasma sodium