Test Your Knowledge: Hyponatremia in Pregnancy

Hyponatremia in pregnancy is not uncommon, but may on occasion be severe enough to warrant a thorough evaluation and intervention. In a recent case published in AJKD, Pazhayattil and colleagues report a relatively rare cause of hyponatremia and discuss the diagnostic and therapeutic approach to this tricky problem, which can have serious consequences if unrecognized. The following questions based on the article will test your knowledge on this topic.

1. A 10% reduction in effective circulating fluid volume is required before AVP release is stimulated.
   A. True
   B. False

2. A fall in serum sodium concentration of ~5 mEq/L and serum osmolality of ~10 mmol/kg occurs early in pregnancy, and nadir at about 8-10 weeks gestation. The cause(s) of this physiologic change include (choose one or more answer):
   A. Pregnant women are thirsty and ingest more water than solutes, resulting in hyponatremia
   B. Hyponatremia is an artifact, and the true serum sodium concentration in pregnancy is normal
   C. Hyponatremia is the result of a reset osmostat for AVP release
   D. Hyponatremia is due to non-osmotic release of AVP due to arterial underfilling
   E. Increased vasopressinase activity from the placenta results in a breakdown of AVP

3. The treatment of choice for transient diabetes insipidus of pregnancy is:
   A. AVP
   B. Desmopressin
   C. Tolvaptan
   D. Demeclocycline
   E. Either desmopressin or AVP

4. Euvolemic hypotonic hyponatremia in pregnancy can be caused by reset osmostat, true SIADH, and nephrogenic syndrome of antidiuresis (NSIAD). NSIAD is characterized by (choose one or more answers):
   A. Release of AVP at lower sodium concentration than normal, resulting in hyponatremia
   B. Elevated and non-suppressible AVP concentrations, with high urine osmolality
   C. Is an inherited condition with variable manifestations in females
   D. Results from a constitutionally activated V2 receptor, with high urine osmolality even in the absence of AVP secretion

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Solutions to eAJKD’s Test Your Knowledge: Hyponatremia in Pregnancy
Based on Pazhayattil et al AJKD teaching case

1. A. True
As explained by Pazhayattil et al, AVP is released in response to osmoreceptors in the hypothalamus/pituitary, and tightly maintains the serum osmolality in the range of 280-290 mOsm/kg. In addition, AVP is also released in response to non-osmotic stimuli. A significant decrease in blood pressure sensed by the baroreceptors will also trigger AVP release. Clinically, this is the explanation behind the hyponatremia associated with congestive heart failure.

2. C&D. C. Hyponatremia is the result of a reset osmostat for AVP release; D. Hyponatremia is due to non-osmotic release of AVP due to arterial underfilling
The reset osmostat phenomenon leading to AVP release and thirst activation at a lower serum osmolality has been described in rat models of pregnancy and also in humans. In addition, Pazhayattil et al note that decreased effective circulating fluid volume may occur from nausea and vomiting in the first trimester as well as relative arterial underfilling due to the systemic vasodilation from hormonal changes (relaxin, estrogen). Vasopressinase is a cysteine aminopeptidase produced by the placental tissue that breaks down endogenous AVP and can result in transient diabetes insipidus and hyponatremia.

3. B. Desmopressin
Transient diabetes insipidus of pregnancy is caused by increased expression of vasopressinase from the placenta. This results in a greater breakdown of vasopressin. Desmopressin (DDAVP), however, is not a substrate for this enzyme and remains effective. Tolvaptan is a vasopressin antagonist and will act as an aquaretic, thus exacerbating diabetes insipidus. It is a category C drug for use in pregnancy. Demeclocycline inhibits adenylate cyclase activity, which is downstream of AVP binding to the V2 receptor and has been described as correcting hyponatremia in SIADH. However, it is potentially nephrotoxic with variable efficacy. It is a category D drug in pregnancy due to its effect on skeletal formation, and should not be used.

4. C&D. C. Is an inherited condition with variable manifestations in females; D. Results from a constitutionally activated V2 receptor, with high urine osmolality even in the absence of AVP secretion
Option A refers to a reset osmostat and option B to SIADH. As Pazhayattil et al explain, the relation of AVP release to serum osmolality is completely normal in NSIAD.
However, the mutation in the V2 receptor results in constitutive activation, even in the absence of AVP. This causes a high urine osmolality (and corresponding hyponatremia) even in the absence of AVP. NSIAD can affect both males and females, but in females the clinical manifestation varies due to the hemizygous state and variable lyonization of the X chromosome.