Systemic Arterial Vasodilation, Vasopressin, and Vasopressinase in Pregnancy

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ABSTRACT

Systemic arterial vasodilation in early pregnancy is accompanied by a compensatory rise in cardiac output and a decline in BP. This relative arterial underfilling in early pregnancy is coupled to stimulation of the renin-angiotensin-aldosterone system and hypotonicity. Arterial underfilling induces the nonosmotic stimulation of arginine vasopressin and upregulation of aquaporin 2 followed by trafficking of this water channel to the apical membrane of principal cells along the collecting ducts. In middle and late pregnancy, there also is a four-fold increase in vasopressinase, a cystine aminopeptidase produced by placental trophoblasts, which enhances the metabolic clearance of vasopressin. In the setting of preeclampsia, twins or triplets, or subclinical central diabetes insipidus, a transient diabetes insipidus may ensue from this vasopressinase-mediated degradation of N-terminal amino acids from the vasopressin molecule. Because desmopressin is already deaminated at the N-terminal, it is resistant to the effect of vasopressinase and therefore is the treatment of choice for transient diabetes insipidus of pregnancy.

Systemic arterial vasodilation occurs very early in the first trimester of pregnancy.[1] This change in the arterial circulation happens before maturation of the placenta; therefore, at least early in gestation, arterial vasodilation cannot be explained by arteriovenous shunting through the placenta. Estrogens are known to upregulate nitric oxide (NO) synthase,[2] and there is experimental evidence that NO contributes to this arterial vasodilation during pregnancy.[3,4] Moreover, an increase in circulating relaxin during early pregnancy is also known to increase NO-mediated arterial vasodilation.[5] Systemic arterial vasodilation in pregnancy is associated consequently with a secondary increase in cardiac output.[1] This increase in cardiac output is inadequate, however, to compensate for the arterial vasodilation and diminished systemic vascular resistance. Thus, arterial BP declines during the first trimester of normal pregnancy.

Compensatory responses, in addition to the increase in cardiac output, occur in association with the arterial vasodilation of pregnancy. Specifically, there is evidence that the neurohumoral axis, including activation of renin-angiotensin-aldosterone system, is stimulated early in normal pregnancy.[1] Moreover, administration of an angiotensin-converting enzyme inhibitor lowers BP in the pregnant rat.[6]

The systemic arterial vasodilation in the first trimester of pregnancy is also associated with stimulation of thirst, increased water intake, and a decline in plasma osmolality of approximately 8 to 10 mOsm/kg H_2O (4- to 5-mEq/L decline in serum sodium concentration).[7] In other clinical circumstances of arterial underfilling, whether as a result of a decrease in cardiac output from heart failure or systemic arterial vasodilation as occurs with cirrhosis, increases in the renin-angiotensin-aldosterone system, hypotonicity, and hyponatremia all are common occurrences.[8] The hypotonicity in these edematous disorders, however, is more profound than what occurs in pregnancy. The nonosmotic stimulation of vasopressin clearly is the mediator of the hyponatremia in these edematous disorders, not only by RIA measurements but also by reversal of the hyponatremia with V2 vasopressin antagonists.[9]

A similar nonosmotic stimulation of thirst and release of vasopressin would be expected with the systemic arterial vasodilation of pregnancy. The hypotonicity seen in pregnant rats, which is similar to that observed in human pregnancy, is associated with increased plasma and hypothalamic vasopressin.[3] Because of the modest degree of hypotonicity during pregnancy, a large acute water load (20 ml/kg) may lower plasma osmolality substantially and override the nonosmotic release of AVP, thereby leading to urinary dilution.

There is other evidence for the role of vasopressin in pregnancy. Studies dem-
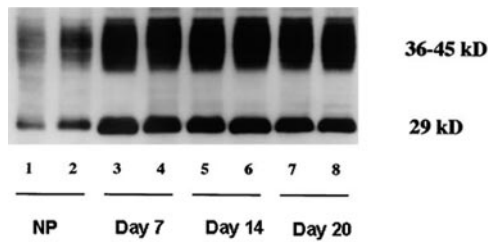
Figure 1. AQP2 protein expression is increased in normal pregnant rats on days 7, 14, and 20 of gestation compared with nonpregnant (NP) rats. Two bands are detectable: A band of 29 kD and a broader band of 36 to 45 kD corresponding to the predicted molecular mass of AQP2 and its glycosylated form. Reprinted from reference[10], with permission.

onstrate that expression of aquaporin 2 (AQP2) water channels in principal cells along the collecting duct are regulated by vasopressin.[10] Thus, the nonosmotic stimulation of vasopressin in rat pregnancy should increase the medullary expression of AQP2 and its trafficking to the apical membrane. This has been clearly demonstrated (Figure 1).[10] These effects on AQP2 during pregnancy are reversed by a V2 vasopressin receptor antagonist. Moreover, urinary AQP2 has been shown to increase in human pregnancy as compared to the nonpregnant state.[11] Thus, the modest lowering of the osmotic threshold for plasma vasopressin in pregnancy seems most likely to be secondary to systemic arterial vasodilation, leading to the nonosmotic stimulation of vasopressin and upregulation of AQP2. This is compatible with the peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy.[12]

There is another very interesting and important event relating to the vasopressin in pregnancy. This is the role of vasopressinase, a cystine aminopeptidase produced by the placental trophoblasts during pregnancy. In previous studies, measurement of plasma vasopressin necessitated the inclusion of an inhibitor of vasopressinase, phenanthroline. Initially, this activity of vasopressinase in degrading vasopressin was believed to be an artifact of *in vitro* analysis. Subsequent studies, however, demonstrated that vasopressinase actively degrades vasopressin *in vivo* during pregnancy. In normal pregnancy, increased synthesis and release of vasopressin is adequate to maintain vasopressin plasma concentrations despite the increased activity of vasopressinase; however, in some pregnancies, increased levels of vasopressinase are associated with a transient diabetes insipidus.[13]

This polyuric state is observed in women carrying multiple pregnancies, perhaps as a result of increased placental trophoblastic synthesis of vasopressinase. Transient diabetes insipidus of pregnancy

also may occur with the liver involvement associated with preeclampsia, perhaps secondary to diminished hepatic degradation of vasopressinase. Moreover, subclinical central diabetes insipidus may become clinically apparent during normal pregnancy, when vasopressin degradation by vasopressinase occurs and an adequate compensatory increase in vasopressin synthesis and release does not. Durr *et al.*[14] performed a seminal study defining the mechanism of vasopressinase-mediated transient diabetes insipidus of pregnancy. Large doses of exogenous vasopressin (up to 75 µg or 30 IU intravenously) were ineffective in treating this polyuria of pregnancy. The polyuria—up to 25 L/d—responded, however, to the administration of dDAVP. Bioinactive fragments of vasopressin appeared with this vasopressinase-mediated diabetes insipidus of pregnancy. Vasopressinase degrades vasopressin by sequentially removing amino acids from the N-terminus. Because dDAVP, desmopressin, is deaminated at the N-terminus, the degradative effect of vasopressinase does not occur with exogenous dDAVP. Thus, dDAVP is the treatment of choice for the transient diabetes insipidus of pregnancy, which is caused by excessive vasopressinase and/or the inadequate response of vasopressin synthesis during pregnancy.

Studies of normal women by Davison *et al.*[15] examined the plasma vasopressin concentrations, urine osmolality, vasopressinase activity, metabolic clearance of vasopressin, and effect of dDAVP during pregnancy *versus* the postpartum period. Plasma levels of vasopressin and urine osmolality were
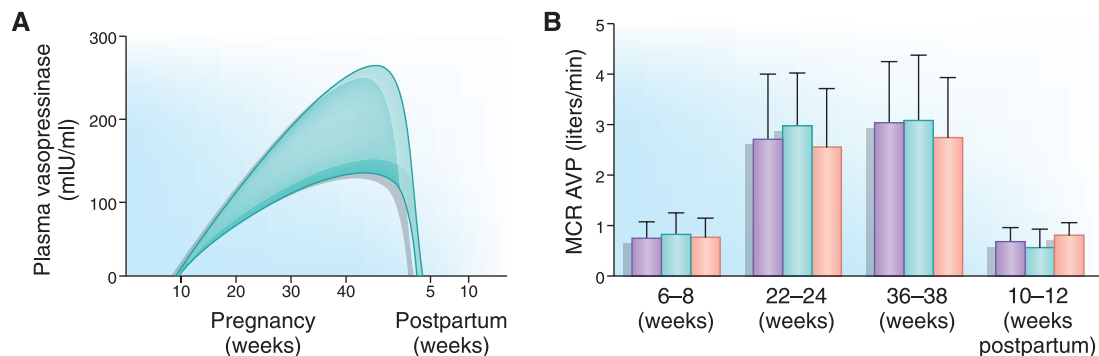

Figure 2. (A and B) Plasma vasopressinase activity (A) and vasopressin metabolic clearance rate (B) during pregnancy are shown. Adapted from reference[15], with permission.

no different between these two periods; however, the metabolic clearance rate of vasopressin was four-fold increased during middle (22 to 24 wk) and late (36 to 38 wk) pregnancy and returned to normal in the 10 to 12 wk postpartum (Figure 2). This increase in the metabolic clearance of vasopressin is associated with increased vasopressinase activity, which returns to undetectable levels in the postpartum period. The marked increment in the rate of metabolic clearance of vasopressin occurs between weeks 7 and 8 of pregnancy through midpregnancy. This is the period of the largest rise in trophoblast mass and plasma vasopressinase activity. The vasopressinase activity increases 40- to 50-fold in middle and late pregnancy using either an enzymatic or a photometric method. The trophoblastic mass in pregnancy is estimated to increase 1000-fold between gestational weeks 6 and 24 and to plateau thereafter.[16] Moreover, because vasopressinase cannot degrade dDAVP, the metabolic clearance rates of dDAVP were no different when comparing middle and late pregnancy with the postpartum period.[15]

ACKNOWLEDGMENTS

DISCLOSURES

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