Adrenal Diseases During Pregnancy: Pathophysiology, Diagnosis and Management Strategies

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Abstract: Adrenal diseases—including disorders such as Cushing's syndrome, Addison's disease, pheochromocytoma, primary hyperaldosteronism and congenital adrenal hyperplasia—are relatively rare in pregnancy, but a timely diagnosis and proper treatment are critical because these disorders can cause maternal and fetal morbidity and mortality. Making the diagnosis of adrenal disorders in pregnancy is challenging as symptoms associated with pregnancy are also seen in adrenal diseases. In addition, pregnancy is marked by several endocrine changes, including activation of the renin-angiotensin-aldosterone system and the hypothalamic-pituitary-adrenal axis. The aim of this article was to review the pathophysiology, clinical manifestation, diagnosis and management of various adrenal disorders during pregnancy.

Key Indexing Terms: Pregnancy adrenal disease; Cushing's syndrome; Adrenal insufficiency; Pheochromocytoma; Primary hyperaldosteronism; Congenital adrenal hyperplasia. **[Am J Med Sci 2014;347(1):64–73.]**

Adrenal diseases—including disorders such as Cushing's syndrome (CS), adrenal insufficiency (AI), pheochromocytoma, primary hyperaldosteronism (PHA) and congenital adrenal hyperplasia (CAH)—are relatively rare in pregnancy, but a timely diagnosis and proper treatment are critical because these disorders can cause maternal and fetal morbidity and mortality.[1,2] They may manifest for the first time during pregnancy or before pregnancy undiagnosed or diagnosed and treated. They may present with either hormonal hypofunction or hyperfunction.[2] Making the diagnosis of adrenal disorders in pregnancy is challenging as symptoms associated with pregnancy are also seen in adrenal diseases. In addition, the fetal-placental unit alters the maternal endocrine function and hormonal feedback mechanisms and the renin-angiotensin-aldosterone (RAAS) undergoes various changes during pregnancy.[1,2]

The aim of this article was to review the pathophysiology, clinical manifestation, diagnosis and management of various adrenal disorders during pregnancy.

HYPOTHALAMUS-PITUITARY-ADRENAL AXIS PHYSIOLOGY IN NORMAL PREGNANCY

Adrenal Steroidogenesis

Pregnancy is associated with marked changes in the hypothalamus-pituitary-adrenal (HPA) axis, resulting in a state of increasing HPA function. The fetoplacental unit has a marked steroidogenic capacity, causing 2-fold to 3-fold increase in maternal plasma cortisol concentrations during pregnancy, and these concentrations may overlap those seen in CS.[3] The increases in plasma cortisol are noted as early as 11 weeks of gestation (Figure 1).[4] Furthermore, placental estrogen production enhances release of cortisol binding globulin (CBG) from the liver, leading to an increase in total cortisol concentrations and a decrease in cortisol clearance. With displacement of cortisol from CBG by progesterone, plasma-free cortisol concentrations also rise.[4,5] Salivary cortisol, another measure of plasma-free cortisol, is more than 2-fold increase compared with nonpregnant controls in the third trimester. Pregnancy is indeed considered to be a natural variant of hypercortisolism. Plasma 17 hydroxysteroids rise during pregnancy as well.[2]

Plasma adrenocorticotropic hormone (ACTH) concentrations rise dramatically through pregnancy, with a surge during labor and delivery, followed by a rapid decrease within 2 days postpartum (Figure 1).[4] Placentally derived ACTH may be a potential contributor to hypercortisolism in pregnancy. Similarly, placental corticotropin-releasing hormone (CRH) rises several 100-fold during pregnancy, reaching very high concentrations at term[1,2,6] (Figure 2). In contrast to CS and despite this state of HPA axis activation, the normal maternal diurnal variation of plasma cortisol is maintained throughout pregnancy.[1,2,7]

Renin-Angiotensin-Aldosterone System

Human pregnancy induces many changes in the RAAS (Figure 3). Many studies have shown that in normal pregnancy, there is an increase in almost all of the components of the RAAS.[9] There is an early increase in renin concentrations because of extrarenal renin secretion by the ovaries and maternal decidua and the stimulatory effect of estrogen on the renal renin release (Figure 4).[10] Angiotensinogen synthesis by the liver is increased by the increased estrogen concentrations. This leads to increase in serum angiotensin II and aldosterone concentrations (Figure 5).[2,8,11,12] Deoxycorticosterone, a potent mineralocorticoid, increases from 2-fold normal in early pregnancy to more than 100 ng/dL in the third trimester (Figure 5), which may contribute to sodium retention of pregnancy.[2,12,13]

Progesterone, concentrations of which are markedly increased in pregnancy, is a competitive inhibitor of aldosterone in the distal tubule. It reduces sodium reabsorption and also contributes to reduced systemic vascular resistance. Therefore, the physiological effects of increased aldosterone are attenuated in pregnancy.[2] Progesterone also demonstrates an antikaliuretic effect, and therefore, hypokalemia may be ameliorated during pregnancy in women with PHA.[14]

Control of the Adrenal Cortex

In contrast to the usual negative feedback action of cortisol in the hypothalamus, there is increased production in placental CRH in response to cortisol (Figure 6).[15] The effect of placental CRH on maternal pituitary is unclear.[16] Placental ACTH is shown to be stimulated by CRH and seems to be

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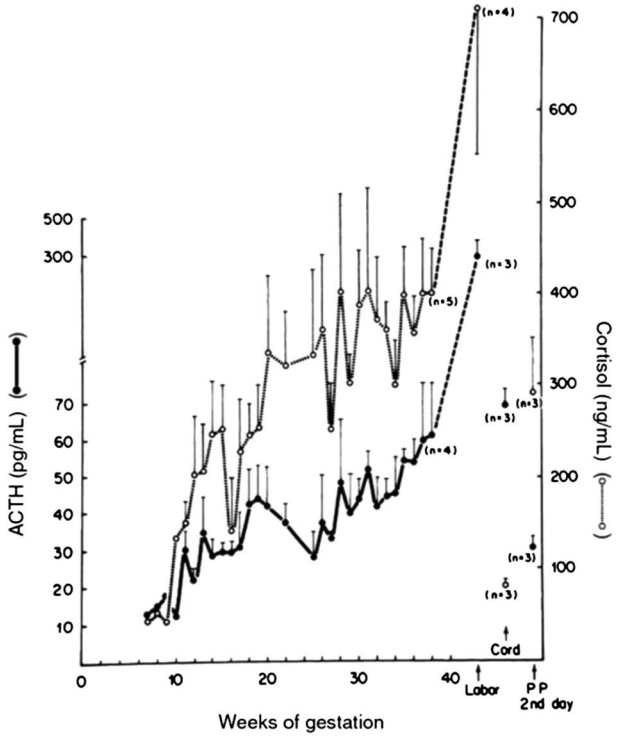

FIGURE 1. Serial increases in serum cortisol (○) and ACTH (●) during pregnancy in normal controls throughout pregnancy. Blood samples were obtained weekly from 5 normal pregnant women and from 3 women during labor and on the second postpartum day. In addition, umbilical cord plasma was obtained from the newborn infants of 3 of these subjects. The vertical bars correspond to the magnitude of the standard error of the mean.[4] Normal concentrations in nonpregnant women: total plasma cortisol: 10 to 25 ng/mL; ACTH: 10 to 60 pg/mL. ACTH, adrenocorticotropic hormone; PP, postpartum.

not suppressible by glucocorticoids. There is also lack of suppression of cortisol after 1-mg dexamethasone because of the high concentrations of bound cortisol and the presence of a state

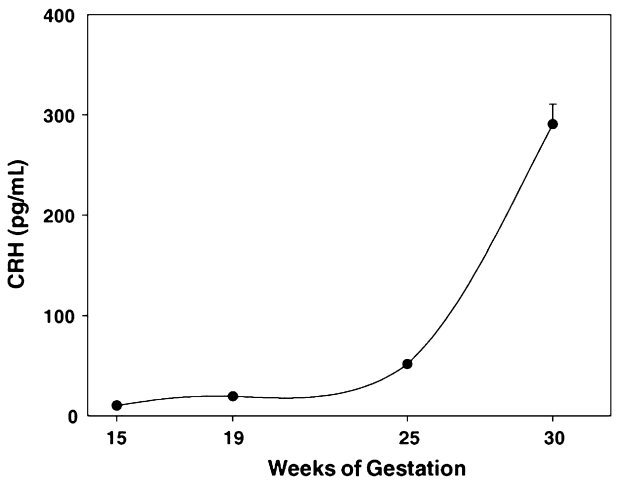

FIGURE 2. Mean plasma CRH concentrations in 203 women followed to term. CRH concentrations increase significantly during pregnancy and show a rapid acceleration after 25 weeks of gestation.[6] CRH, corticotropin-releasing hormone.

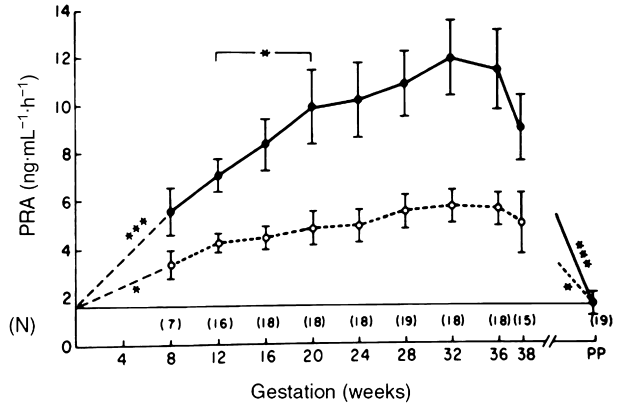

FIGURE 3. Sequential increases in plasma renin activity (mean ± SE) during normal pregnancy and at 4 to 6 weeks postpartum in a sample of 19 women. The data were normalized to postpartum concentrations (control values represented by dashed lines). Values are mean ± SE.[8] Asterisks denote differences in concentrations over time. *$P < 0.05$; ***$P < 0.001$. PP, postpartum; PRA, plasma renin activity.

of "cortisol resistance" induced by elevation of progesterone (Figure 6).[16]

It should also be noted that the fetus is protected in early gestation from the effects of maternal hypercortisolism by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD 2). The latter converts active glucocorticoids—cortisol and corticosterone—to their inactive 11-keto-metabolites.[16] However, in late gestation, there is a reversal of 11β-HSD 2 activity in favor of the active hormone in the uterus that may contribute to fetal lung maturation.[17]

CUSHING'S SYNDROME

CS is uncommon in pregnancy, likely because hypercortisolism results in ovulatory disturbances and relative infertility. To date, approximately 140 cases of CS in pregnancy have been reported.[1]

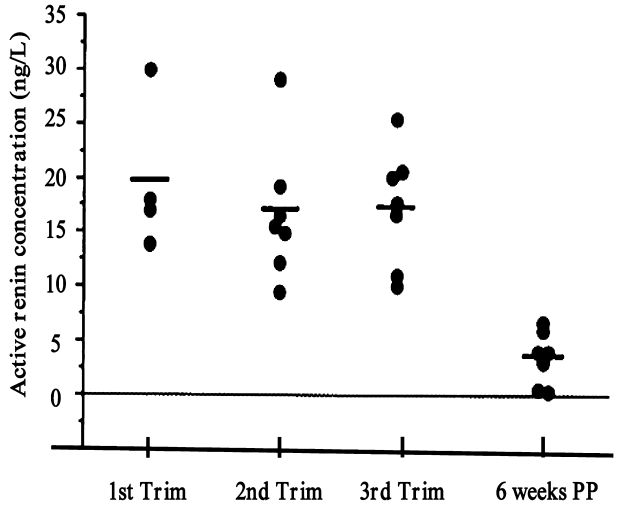

FIGURE 4. Distribution of active renin concentrations during pregnancy and at 6 weeks PP in a sample of 7 normal pregnant women.[10] The short horizontal lines represent the mean value. PP, postpartum.