Management of Adrenal Tumors in Pregnancy

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KEYWORDS

• Pregnancy • Cushing syndrome • Adrenal cell carcinoma • Adrenal tumor
• Pheochromocytoma • Hyperaldosteronism

KEY POINTS

- Adrenal diseases including Cushing syndrome (CS), primary aldosteronism (PA), pheochromocytoma, and adrenocortical carcinoma are uncommon in pregnancy; a high degree of clinical suspicion must exist.
- Physiologic changes to the hypothalamus-pituitary-adrenal axis in a normal pregnancy result in increased cortisol, renin, and aldosterone levels, thus making the diagnosis of CS and PA in pregnancy challenging. However, catecholamines are not altered in pregnancy and allow a laboratory diagnosis of pheochromocytoma that is similar to that of the nonpregnant state.
- Although adrenal tumors in pregnancy result in significant maternal and fetal morbidity, and sometimes mortality, early diagnosis and appropriate treatment often improve outcomes.

INTRODUCTION

Adrenal diseases, including Cushing syndrome (CS), primary aldosteronism (PA), pheochromocytoma, and adrenocortical carcinoma (ACC), are uncommon in pregnancy. Normal physiologic changes to the hypothalamus-pituitary-adrenal (HPA) axis during pregnancy result in a physiologic hypercortisol state and changes in the renin-aldosterone-angiotensin system (RAAS) result in increased renin and aldosterone production in healthy pregnant women. Normal pregnant women are able to overcome these hormonal changes without adverse consequences, but such changes pose a challenge to the diagnosis of a disease state in pregnancy. Undiagnosed CS,

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PA, pheochromocytoma, and ACC contribute to significant maternal and fetal morbidity and mortality. This article reviews the normal changes to the HPA axis in pregnancy and describes the diagnosis and management of adrenal disease during pregnancy.

Changes to the Hypothalamus-Pituitary-Adrenal Axis in Pregnancy

Changes in the HPA axis and the RAAS in pregnancy result in an increase in activity of both systems. Although the size and weight of the adrenal gland remain similar to the nonpregnant state, the zona fasciculata, the mostly cortisol-producing zone of the adrenal gland, is reported to increase in pregnancy.[1,2]

Hypothalamic-pituitary-adrenal axis

In healthy women, total and free plasma cortisol, adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), cortisol binding globulin (CBG), and urinary free cortisol (UFC) all increase in pregnancy. Placental CRH is similar to hypothalamic CRH,[3] although it does not follow a circadian pattern.[4] Placental CRH stimulates the placenta to produce ACTH,[5] which in turn stimulates the maternal adrenal glands to produce cortisol. In addition, the maternal adrenal glands are more responsive to ACTH during pregnancy,[6] resulting in an increase in free serum cortisol levels and UFC.[3] Although much of placental ACTH production is autonomous[7] and fails to respond to the negative feedback of glucocorticoids,[8] maternal serum cortisol has a positive feedback on placental CRH, further increasing its levels.[9] Placental CRH may also stimulate the maternal pituitary to release ACTH.[10] Estrogen from the placenta also plays a role by stimulating the production of CBG from the liver, resulting in increased bound and total serum cortisol levels. Progesterone from the placenta may have an antiglucocorticoid effect that contributes to the increase in free cortisol as well, because it creates a state of relative glucocorticoid resistance.[11] In addition, there may be an altered set point for pituitary ACTH response to cortisol feedback, with tissues more refractory to cortisol (**Box 1**).[6,7]

Although the initial increase in CBG early in pregnancy produces a transient reduction in free cortisol level, maternal ACTH levels increase in response, resulting in a normal cortisol level early in pregnancy[3] and increasing cortisol levels at as early as 11 weeks gestation.[12] A progressive increase has been described in total and free plasma cortisol, CBG, and 24-hour UFC levels throughout each trimester with free cortisol levels increasing by 1.2-fold, 1.4-fold, and 1.6-fold, and with 24 hour UFC level increasing 1.7-fold, 2.4-fold, and 3.1-fold compared with a control group in the first, second, and third trimesters respectively.[13] Maternal serum CRH, derived mostly from the placenta, becomes detectable then steadily begins to increase starting in the middle of the second trimester, with a sharp upswing at the end of gestation.[14,15] ACTH values also increase throughout pregnancy beginning in the late first trimester and peaking during labor and delivery.[16,17] CRH and ACTH levels return to nonpregnant values within 24 hours of delivery.[18] At 2 to 3 months postpartum, plasma free cortisol and UFC levels return to baseline but CBG and total plasma cortisol levels remain increased.[13] Although cortisol levels increase throughout pregnancy, diurnal variations of cortisol remain in pregnancy, but with a higher evening nadir.[4,6,12]

Renin-angiotensin-aldosterone system

Maternal progesterone levels increase throughout gestation, mostly as a result of placental progesterone production.[19] Progesterone acts as an antagonist to the mineralocorticoid receptor, likely at the renal tubule level.[20] This process results in an increase in sodium secretion[20] and an increase in aldosterone production.[21] This