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Review article

The adrenal cortex: Physiology and diseases in human pregnancy

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ABSTRACT

Pregnancy is characterized by marked alterations in the hypothalamic–pituitary–adrenal axis and in the function of the adrenal gland. Some of those alterations have clinical characteristics that are similar to those of adrenal gland disorders.

While adrenal disorders are rare among pregnant women, they harbor the potential for significant morbidity if they remain unrecognized and untreated. As the majority of patients with adrenal disorders present with clinical features that are typical of normal pregnancy - diagnosis during pregnancy is not uncommonly delayed. A high index of suspicion must be practiced for these disorders as they might carry severe obstetrical negative outcomes. In this review we will survey the normal function of adrenal glands in pregnancy and the role of adrenal hormones in pregnancy. We will outline the adrenal disorders that commonly present during pregnancy and review the literature on treatment modalities.

Contents

Introduction

Pregnancy is characterized by substantial changes in a number of endocrine systems, particularly in the hypothalamic–pituitary–adrenal axis and the renin–angiotensin–aldosterone system [1,2].

Adrenal gland disorders are uncommon in pregnancy. Nevertheless, adrenal deficiencies and excesses can be associated with considerable fetal and maternal morbidity [3,4]. Diagnosis is challenging since clinical features are similar to normal characteristics of pregnancy, and the fetal-placental unit alters maternal endocrine metabolism and feedback [5]. Therefore, a high index of suspicion and timely diagnosis is of utmost importance.

The aim of this review is to survey the adrenal disorders most commonly occurring during pregnancy and to discuss approaches to their diagnosis and treatment during pregnancy.

Changes during pregnancy

Adrenocorticotrophic hormone (ACTH) is secreted by the anterior pituitary in response to hypothalamic-releasing factor corticotropin-releasing hormone (CRH), which further stimulates the release of adrenal glucocorticoids [2,6]. ACTH secretion has a marked diurnal variation, with an early morning peak and a late

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evening nadir [7]. As with the other pituitary hormones, ACTH secretion is negatively regulated by feedback from the end product hormone secreted from the adrenals – cortisol [4].

Pregnancy is a state of increased demand for steroid production, to meet the need for increased maternal production of estrogen and cortisol, and the fetal need for somatic and reproductive growth development. During pregnancy, marked changes occur in adrenocortical function, resulting in increased serum levels of ACTH, cortisol, aldosterone, deoxycorticosterone and corticosteroid-binding globulin (CBG), thus, a state of physiologic hypercortisolism is maintained during pregnancy [5,8].

The adrenal gland does not increase significantly in weight during pregnancy, in contrast to the marked expansion in size of the zona fasciculata, the main production source for glucocorticoids.

Most binding globulins increase during pregnancy, due to increased hepatic production stimulated by increased levels of estrogen; likewise, CBG nearly doubles. This results in elevated total plasma cortisol. Total cortisol levels at the end of pregnancy are nearly threefold normal levels, thus simulating a state that resembles the Cushing syndrome. The increased production of CBG does not explain the increased levels of free cortisol observed in pregnancy. Free cortisol, the fraction of cortisol that is not bound to CBG, is the only metabolically active cortisol compound. The rise in free cortisol is evident by increased urinary free cortisol concentrations and salivary cortisol concentrations, and can be measured using the free cortisol index [9–11]. In fact, urinary free cortisol concentration doubles from the first to the third trimester of pregnancy [12]. This seems to be caused mainly by a marked increase in CRH secretion during pregnancy, which in turn stimulates the production of ACTH in the placenta and the pituitary [13,14]. Though CRH is mainly secreted from the hypothalamus, increased CRH serum levels during pregnancy are due in large part to production by placental and fetal membranes, which secrete CRH that reaches the maternal circulation. This rise in CRH drives the increased levels of cortisol observed in pregnancy. After the second trimester, CRH rises exponentially, predominantly as a result of placental production. Serum levels of CRH and ACTH continue to rise in the third trimester despite the increased levels of total and free cortisol [15]. While this phenomenon is consistent with the main role of placental CRH secretion [16,17], other plausible explanations for the state of hypercorticolism include pituitary desensitization to cortisol feedback, changes in plasma clearance of cortisol as a result of changes in renal function and enhanced pituitary responses to vasopressin and CRH [8].

The hypercorticolism levels of cortisol during pregnancy are expressed clinically by maternal tiredness, weight gain, hyperglycemia, edema and emotional upset. Since these are normal characteristics of pregnant women, diagnosing Cushing syndrome during pregnancy is challenging.

Another important adrenal product is deoxycorticosterone (DOC), which resembles aldosterone, and has a potent mineralocorticoid. A marked rise in serum DOC is observed from the first trimester. Unlike in the non-pregnant state, plasma DOC in late pregnancy does not respond to external manipulations such as increased salt intake, dexamethasone suppression and ACTH stimulation [8]. Again, this independent state of increased hormone levels suggests an autonomous source of DOC secretion, presumably the placenta or fetal membranes.

Other adrenal hormonal changes encountered in pregnancy are a slight increase in testosterone due to an increase in sex hormone binding protein synthesis by the liver, a slight rise in androstenedione due to increased adrenal synthesis and a decrease in dehydroepiandrostendione sulfate levels in light of increased renal clearance of the hormone. In addition to these changes, marked increases during pregnancy, of up to sevenfold, are observed in aldosterone, angiotensin II and plasma renin activity [18]. This upregulation of the renin-angiotensin system increases sodium retention and plasma volume, mainly by the high circulating aldosterone levels, and maintains normal blood pressure in the setting of gestational vasodilation. A particular phenomenon can occur in pregnancy, which is dissociation of renin and aldosterone levels, such that aldosterone levels are higher than expected in relation to renin levels, compared to the non-pregnant state; again, this is achieved by a high responsiveness of the adrenal gland to angiotensin II [19,20].

Cushing syndrome

Cushing syndrome in pregnancy is hardly reported and represents a true rarity. As few as 150 cases have been described; the etiology of most of them were pituitary and adrenal adenomas, and about 10% were cases of adrenal carcinoma. The entity of an ectopic secretion of ACTH is extremely rare and scarcely reported [1,21–25]. Interestingly, human chorionic gonadotropin (hCG) stimulation of ectopic luteinizing hormone/hCG receptors on the adrenal gland have also been reported [25].

As previously described, the diagnosis of Cushing syndrome during pregnancy is difficult due to the similarity between the two states in clinical presentation. Clinical suspicion should arise when proximal myopathy and bone fractures occur. Consistent with the similarities in clinical presentation to normal pregnancy, non-distinctive laboratory findings augment the challenge of differentiating between the conditions. The overnight dexamethasone suppression test shows inadequate suppression and increased levels of total and free cortisol and of ACTH, as in pregnancy [2,22–24,26]. Moreover, midnight levels of salivary cortisol during pregnancy have yet to be set [21]. The most helpful discriminating finding is the persistent circadian variation in the elevated levels of total and free serum cortisol, which remains in normal pregnancy and is absent in the Cushing syndrome [2,7]. Imaging modalities are not applicable to Cushing diagnosis during pregnancy as magnetic resonance imaging without contrast of the pituitary is questionable and ultrasound scan of the adrenals may identify a substantial proportion of incidental findings known as "incidentalomas" [27,28]. Other modalities of evaluation such as petrosal venous sinus sampling and CRH stimulation testing have been scarcely reported [24,26].

Cushing syndrome carries a substantial risk for pregnancy loss. The outcomes of almost 25% of cases are miscarriage, intrauterine fetal demise or severe prematurity [21,22]. Suppression of fetal adrenal may also occur, as a result of placental transfer of cortisol to fetal circulation [29]. Complications associated with the development of hypertension (e.g. pregnancy hypertensive disorders) and diabetes also present during pregnancy. Moreover, post-cesarean wound complications are common [30]. Prevention of pregnancy loss by initiation of treatment has been suggested by some [1,21]. Accordingly, the live birth rate was described to increase from 76% to 89% when treatment was initiated by an estimated gestational age of 20 weeks. The main question is the acceptability of treatment during pregnancy. Ketoconazole has been associated with intrauterine growth retardation and liver toxicity [1], and hence is not recommended. The efficacy of metyrapone in pregnancy is questionable [21] and mitotane should be avoided due to fetal toxicity. Mifepristone, which is commonly prescribed in obstetrics and gynecology, should also be avoided [31], as it interferes with progesterone bioactivity. Pasireotide, a somatostatin analogue, should only be used in an experimental setting due to the lack of evidence on its safety during pregnancy [32], and its role in provoking the hyperglycemic state. Surgical management of the different etiologies of Cushing syndrome has been

described; these include successful laparoscopic resection of adrenal adenomas and laparoscopic resection of adrenal adenomas during the second trimester [21]. When laparoscopic adrenalectomy is performed during the second trimester, the live birth rate approximates 87% [1] and the benefits of surgical treatment probably outweigh the risks of the procedure and of procedure avoidance [33].

Adrenal insufficiency

The main cause of adrenal insufficiency in the western world is autoimmune adrenalitis. Less common etiologies are infectious causes (e.g. tuberculosis, fungi), metastatic spread of neoplasm and vascular accidents. Secondary adrenal insufficiency may also arise due to pituitary neoplasms or pituitary suppression [34,35]. As in hypercorticolism, many of the clinical features of adrenal insufficiency are common in normal pregnancy, such as weakness, vomiting, hyponatremia, syncope and hyperpigmentation. Clinical features that might raise suspicion for adrenal insufficiency are weight loss, extreme hyponatremia, hypoglycemia and salt craving. As the placenta and fetus each control their own steroid environment, maternal adrenal insufficiency hardly causes any harm to fetus development. Nevertheless, a maternal adrenal crisis may appear during stress, such as a urinary tract infection or labor [36,37]. The main laboratory evaluation may be remarkable for hyponatremia, hyperkalemia, hypoglycemia, eosinophilia and lymphocytosis. Diagnosis can be confirmed by early morning plasma cortisol levels of 3.0 μg/dL (83 nmol/L) or less, or by the cosyntropin test. The 1-μg low-dose cosyntropin test has been reported to be accurate at midgestation, using a cutoff of 30 μg/dL (828 nmol/L) [38]. However, ACTH is not low in secondary forms due to placental production of this hormone. The effects of Addison disease on pregnancy are mainly an increased risk for prematurity, low birth weight and an increased risk for cesarean delivery [39]. The optimal glucocorticoid replacing dose during pregnancy is not well established, and continuous adjustment should be anticipated. An increase by up to 40% from baseline dose is usually necessary after the 24th week of gestation. Hydrocortisone should be used as it does not cross the placenta [40]. Mineralocorticoid replacement is somewhat less needed during pregnancy, as progesterone shows anti-mineralocorticoid properties. Dose requirements are monitored by evaluating blood pressure in the sitting and standing positions, and by evaluating blood electrolytes [41]. When maternal status is unbalanced (severe hyponatremia or acidosis), poor fetal outcome may ensue [36,37,39]. Due to the potentially severe consequences and complications, commencing with empiric glucocorticoid therapy of intravenous hydrocortisone 50 to 75 mg is of utmost importance when diagnosis of adrenal insufficiency is suspected in an unstable patient. After diagnosis, in times of stress (e.g. infection) and labor, doses of up to 75 mg every 6 to 8 h should be administered [37]. During delivery, a dose of 100 mg should be commenced before onset of active labor, followed by continuous infusion of up to 300 mg per hour [41]. In the early postpartum period, twice the maintained dose administered during pregnancy is needed. After 48 h, the dose can be reduced to the pre-gestation level. When labor nears, the question of iatrogenic adrenal suppression due to glucocorticoid treatment in inflammatory diseases must be addressed. These patients are presumed to have adrenal axis suppression for at least 12 months following cessation of such therapy [42] and should receive a stress dose as previously described.

Pheochromocytomas

Pheochromocytomas originate from the adrenal medulla [43]. Abnormally elevated levels of catecholamines produced by tumors result in elevated blood pressure (paroxysmal or sustained), palpitations, headache and diaphoresis. Syncope and orthostatic hypotension are also common and are indicative of the diagnosis [44]. As hypertensive disorders of pregnancy are far more common than pheochromocytoma, the diagnosis of pheochromocytoma is elusive and most often delayed. When left undiagnosed, end organ damage may occur, manifested by ischemic heart disease, stroke, arrhythmia, cardiomyopathy or placental abruption. Pregnancy poses particular characteristics, which have a mass effect on tumor lesions, such as uterus mechanical pressure, fetal movements and uterine contractions; these may cause an intermittent hypertensive crises resulting in fetal hypoxia and demise [44,45]. Diagnosis follows magnetic resonance imaging, which outperforms ultrasonography as pregnancy advances [46,47].

Treatment for pheochromocytoma is based on both alpha- and beta-adrenergic blockade prior to operative treatment. Stabilization of blood pressure and heart rate for a period of 14 days prior to surgery is recommended; treatment with alpha blockers (doxazosin / prazocin) is recommended for 5–7 days, followed by beta blockers (propranolol) [48]. The surgical approach is dependent on gestational age and is influenced by the gravid uterus; in early pregnancy, the laparoscopic approach is advocated, while in late gestation – open laparotomy may achieve better exposure [45]. The mode of delivery before complete surgical resolution is achieved is debatable, as both vaginal and cesarean delivery have been described, with comparable outcomes [49,50].

Primary hyperaldosteronism

Primary hyperaldosteronism (PA), an oversecretion of aldosterone by the adrenal gland, is currently the leading cause of secondary hypertension. While 0.6-0.8% of pregnant women are estimated to have PA, the literature is scarce [51]. As with other adrenal disorders, the diagnosis of PA during pregnancy is challenging due to the physiological changes of the renin angiotensin system during this period. This is further complicated by the development of gestational hypertensive disorder in up to 10% of pregnant women. High aldosterone levels are not diagnostic; however, low renin concentrations may direct the diagnosis towards PA, and the aldosterone-renin ratio can likely aid the diagnosis. As progesterone is a competitive inhibitor of aldosterone in the distal convoluted tubule of the kidney, PA can be masked during pregnancy and be revealed postpartum [52]. The following characteristics may also aid the diagnosis: hypokalemia associated with hypertension, very high levels of aldosterone and low levels of renin, and an adrenal nodule on imaging. The course of PA during gestation varies from clinical improvement to deterioration; data are scarce to support counseling. The anti-mineralocorticoid effect of progesterone might contribute to the clinical improvement observed, thus returning renin and potassium levels, and blood pressure to within normal limits [53]. A number of recommendations are available regarding management of PA in relation to pregnancy. PA should be controlled as optimally as possible before conception; and adrenalectomy is advocated prior to conception if aldosterone secretion is unilateral. Spironolactone should be discontinued and treatment should be undertaken by beta blockers and alpha methyldopa. Diuretics should not be used as maintenance therapy during pregnancy, but rather added if uncontrolled hypertension is encountered [54].

Congenital adrenal hyperplasia

Reduced enzymatic activity at different stages of adrenal steroid biosynthesis results in reduction in cortisol production, and in many cases, in the reduction of aldosterone production. Compensatory increases in CRH and ACTH ensue, and overproduction of

steroid precursors not metabolized by the affected enzyme occurs. More than 95% of cases result from 21-hydroxylase deficiency due to mutations in the CYP21A2 gene; other cases are mostly due to 11-beta hydroxylase deficiency [55]. Management of these women during gestation does not change, except at times of stress (e.g infection, hyperemesis gravidarum, delivery, etc.). Monitoring therapy, which in the non-pregnant state is performed by testosterone, androstenedione and 17-OH progesterone levels, is difficult in pregnancy due to hormonal changes. Some clinicians monitor the bioavailable testosterone levels, whereas others follow the clinical course [56]. Usually, the mineralocorticoid dose does not need to be increased, despite the high levels of progesterone that may compete with mineralocorticoids for the mineralocorticoid receptor. Of note, hyper-secreted androgens are metabolized by the placental aromatase to estrogen, thus preventing fetal exposure. In the rarity of severe non-compliance to treatment, this aromatase can be saturated, causing masculinization in the fetus [57]. There is no evidence for substantial increases in hypertension or diabetes during pregnancy, albeit cesarean delivery is usually performed, especially in the setting of previous extensive genital reconstruction surgery [58]. The role of prenatal dexamethasone, a therapy that prevents virilization of the external genitalia of the affected female infant, is well established. If the fetus is an affected female, dexamethasone should be continued until term. Otherwise, dexamethasone should be discontinued [58].

Conclusion

Diagnosing adrenal disorders during pregnancy is challenging. A careful diagnostic approach to these disorders, including laboratory work-up, must be tailored specifically to pregnancy. No current guidelines are available for managing these patients; rather, recommendations are based on experience and small case series. Although these have served as important sources for the diagnosis and treatment of these disorders, further study is imperative.

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