Adrenal diseases in pregnancy

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Endocrine changes during pregnancy

- considerable endocrine changes

- the fetoplacental unit, accounts for a variety of these changes
Estrogen production during pregnancy

- Large quantities of estrogen are produced after the first 3-4 weeks of gestation, the placenta produces nearly all of the estrogen.
- The major precursor for estrogen production is dehydroepiandrosterone sulfate, which is synthesized in the fetal adrenal glands.
Steroid circulation in pregnancy

• More than 90% of the estradiol and estriol and 85% or more of the progesterone formed in the trophoblast are secreted into the maternal compartment.

• The net transfer of steroids to maternal blood is approximately 10 times that of the net transfer to fetal blood
Fetal adrenals

- Adrenals of the human fetus at term are as large as those of adults, weighing 8-10g or more.
- Consist by 85% of an inner zone.
- Fetal adrenals near term, secrete 100-200mg of the estrogen precursor daily.
- The total daily steroid production by the adrenals in an unstressed adult is only approximately 35mg daily.
Fetal adrenals

• provide precursors for placental estrogen formation,
• participate in the events that lead to the initiation of labor and to maturation of the fetal lungs.
• a trophic role has been proposed for other hormones, including growth hormone, human chorionic gonadotropin, prolactin, and human placental lactogen
Steroid circulation in pregnancy (2)

- a small amount of cortisol in maternal plasma crosses the placenta, both because the reentry pathway dominates and because cortisol within the trophoblast is converted to cortisone by 11beta-hydroxysteroid dehydrogenase
Steroid circulation in pregnancy (3)

- dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione, and testosterone, do not reach the fetal compartment
- presence of aromatase enzymes of the syncytiotrophoblast that are used for the conversion of C-19 steroids to estrogens.
- protects the female fetus from possible virilization in women who develop androgen-secreting tumors of the ovary during pregnancy
Steroid circulation in pregnancy (4)

- estrogen and progesterone, appears to be formed or secreted by the placenta.
- No evidence indicates that the placenta synthesizes glucocorticoids or mineralocorticoids
Cortisol-ACTH-CBG

- The levels of cortisol in maternal plasma are markedly increased in association with the rise in estrogen production, partly because of a 3- to 4-fold increase in the level of corticosteroid-binding globulin.
- The rate of secretion of cortisol by maternal adrenals is not increased in pregnancy, but the rate of clearance is decreased.
- The corticotropin level is suppressed
- The lowest level of corticotropin is observed early in pregnancy, rising to a maximum between week 26 and term
Renin-Angiotensinogen

- a 4-fold increase in plasma renin activity is evident by the eighth week of gestation.
- Estrogen stimulates the hepatic synthesis of angiotensinogen.
- Estrogen and progesterone, alone or together, stimulate the secretion of renin, which catalyzes the conversion of angiotensinogen to angiotensin I.
Aldosterone

- aldosterone secretion increases during pregnancy.

- Progesterone, levels of which are markedly increased in pregnancy, is a competitive inhibitor of aldosterone in the distal tubule. Therefore, the physiologic effects of increased aldosterone are attenuated in pregnancy.
Addison’s dis in Pregnancy

• Before glucocorticoid replacement therapy pregnancy in patients with adrenal insufficiency was associated with a maternal mortality rate of 35-45%.

• In patients with treated autoimmune Addison disease, conception, fetal development, and delivery should not be problematic.
Addison’s dis in Pregnancy

- The usual glucocorticoid and mineralocorticoid replacement dosages are continued throughout pregnancy.
- Some patients may require slightly more glucocorticoid in the third trimester.
Addison’s dis in Pregnancy

• During labor, adequate saline hydration and 25mg of intravenous (IV) cortisol should be administered every 6 hours

• At the time of delivery or if the labor is prolonged, high-dose parenteral hydrocortisone should be administered (100mg q6h or as a continuous infusion)

• After delivery, the dosage can be quickly tapered to a maintenance dose in 3 days.
Addison’s dis in Pregnancy

- Occasionally, patients develop severe nausea and vomiting in the first trimester and may need intramuscular (IM) dexamethasone at a slightly increased dose (1mg daily).
Addison’s dis in Pregnancy and IUGR

• Maternal cortisol deficiency has been suggested as a possible cause of fetal intrauterine growth restriction.

• Clinical suspicion if fetal growth restriction is associated with abnormally low maternal blood pressure and an unusual increase in skin pigmentation
New onset Addison dis in pregnancy

• is rare in pregnancy,
• but it may present with prolonged vomiting and weight loss.
• adrenal failure should also be added in the differential diagnosis of hyperemesis gravidarum.
Secondary adrenocortical insufficiency

• may occur as a result of hypothalamic or pituitary diseases.
• Primary lymphocytic hypophysitis usually manifests in pregnancy and is associated with pituitary enlargement
Cushings sy. in pregnancy

• slightly over 100 cases of Cushing syndrome in pregnancy have been reported in the literature

• difficult to detect clinically because of the central weight gain, abdominal striae, increased blood pressure, and glucose intolerance associated with normal pregnancy.
Cushings sy. in pregnancy

• Several cases of exacerbation of Cushing syndrome reported.
• In most cases in pregnancy, an adrenal adenoma benign tumor, was the cause of the Cushing syndrome
• Malignant adrenal tumors are rarely observed in association with pregnancy
• in women who are not pregnant pituitary-dependent disease predominates
Cushings sy in pregnancy-diagnosis

• In normal pregnancy morning cortisol levels (mean plus or minus the standard error of mean) of 14.9 ± 4mg/dL at 11 weeks' gestation and 35.2 ±10mg/dL at 26 weeks' gestation; the levels remained elevated until labor and delivery

• Cortisol levels overlap those found in patients with Cushing syndrome;
Cushings sy in pregnancy-dagnosis

- simple overnight low-dose dexamethasone suppression test are inaccurate in the presence of excess estrogen and in pregnancy.
- Random measurement of urinary or plasma cortisol is not helpful
Cushings sy in pregnancy-diagnosis

- midnight cortisol level can still be very helpful in making the diagnosis
- Normal pregnancy demonstrates 50% suppression of the midnight cortisol level compared with the morning cortisol level
- The standard protocols for low-dose (2mg) and high-dose (8mg) dexamethasone tests have been used safely, and interpretation of suppression of 24-hour urine cortisol and plasma cortisol levels seems to yield reliable results
Cushings sy in pregnancy-diagnosis corticotropin levels

- corticotropin levels are not useful in distinguishing between pituitary and adrenal etiologies
- For all forms of Cushing syndrome in pregnancy, corticotropin levels are normal
- or they are high secondary to placental corticotropin production or owing to placental corticotropin-releasing hormone–stimulated pituitary corticotropin production
Cushings sy in pregnancy-diagnosis

• If the corticotropin level is clearly elevated, a pituitary cause must be considered.
• Ultrasonography or magnetic resonance imaging (MRI) may be used to limit radiation exposure to the fetus
Cushing syndrome risks in pregnancy

- Hypertension becomes worse in two thirds of patients.
- **Preeclampsia** or pregnancy-induced hypertension is noted in approximately 10% of patients.
- **Gestational diabetes mellitus** occurs in approximately one third.
- Congestive heart failure associated with severe hypertension occurs in 10%.
Cushing sy risks in pregnancy

- Severe proximal myopathy
- Mental problems ranging from emotional lability
- Psychosis
- Wound breakdown after surgery: vaginal delivery is preferable to cesarean delivery in patients with Cushing syndrome
Cushing sy risks in pregnancy

- Premature delivery occurs in two thirds of cases.
- The overall perinatal mortality rate is 15% of reported cases; half were stillborn
Cushing sy risks in pregnancy-cortisol withdrawal problems

• mother may develop cortisol deficiency after a successful adrenalectomy
• neonate may have cortisol deficiency soon after birth
Treatment of Cushing sy. in pregnancy: Adrenalectomy

- Surgical treatment during pregnancy is safe and significantly reduces fetal losses, premature labor, and maternal morbidity.
- The ideal timing for adrenalectomy- retroperitoneal laparoscopic adrenalectomy is early in the second trimester.
- After adrenalectomy: Immediately on cortisol replacement, continue until the hypothalamic-pituitary-adrenal axis returns to normal.
- Replacement treatment could take several months.
- Weaning from replacement doses should not be attempted until after delivery.
Cushing’s syndrome in pregnancy: ketoconazole

- **Ketoconazole** has been used successfully in 3 patients during pregnancy. One patient had pituitary-dependent Cushing disease.
- Pregnancy and vaginal delivery at 37 weeks' gestation passed uneventfully,
- newborn male infant did not show any congenital malformation and had normal sexual development
adrenal carcinomas in pregnancy

• termination of the pregnancy may be considered so that definitive therapy can be undertaken
• is a rare and severe disease
• associated with poor fetal and maternal outcome
**Primary hyperaldosteronism in pregnancy**

• rare cause of hypertension in pregnancy
• Hypokalemia should be corrected before making a biochemical diagnosis because a low potassium level suppresses aldosterone
• Avoid diuretics, ca-channel blockers and beta blockers to make a diagnosis
Diagnosis of primary hyperaldosteronism in pregnancy

- Normally plasma aldosterone levels rise in pregnancy to the primary hyperaldosteronism range.
- In a healthy pregnancy, plasma renin activity is usually increased, but it decreases in the setting of primary hyperaldosteronism.
Primary hyperaldosteronism diagnosis in pregnancy

- dynamic test that may be used is stimulation of renin production by positioning the patient in an upright posture
- In pregnant patients, prolonged upright posture results in a modest increase in plasma renin activity.
- If the renin activity remains suppressed, this is suggestive of primary hyperaldosteronism
Primary hyperaldosteronism diagnosis in pregnancy

- Ultrasonography
- MRI
Treatment of primary hyperaldosteronism in pregnancy

- If an adrenal adenoma is detected, unilateral adrenalectomy is the treatment of choice
- Aim adrenalectomy during second trimester
Treatment of primary hyperaldosteronism in pregnancy

• goals of medical therapy: adequate control of blood pressure and replacement of potassium

• spironolactone and angiotensin-converting enzyme (ACE) inhibitors, are contraindicated in patients who are pregnant

• **Methyldopa**, beta blockers, and calcium channel blockers have been used with variable outcomes.
Pheochromocytoma in pregnancy

• potentially disastrous for the mother and fetus.
• The main sign of the disease is **hypertension**
• overall maternal and fetal mortality rates decreased to 17% and 26%, respectively
Pheochromocytoma presentation in pregnancy

- symptomatic hypertension that is often severe and fluctuating
- associated headache, perspiration, palpitation, and tachycardia
- Although hypertension is the hallmark for pheochromocytoma, it may not be present in all cases
Pheochromocytoma presentation in pregnancy

• arrhythmias,
• postural hypotension,
• chest or abdominal pain,
• visual disturbance,
• convulsions,
• sudden collapse
Screening of pheos in pregnancy

- All pregnant women with:
  1. hypertension associated with headache,
  2. palpitation, or excessive sweating
  3. with a family history of pheochromocytoma or associated syndromes
Diagnosis of pheo in pregnancy

• No alteration in catecholamine metabolism develops specifically because of the pregnant state

• accurate 24-hour urine collections for catecholamine assay with epinephrine and norepinephrine and their metabolites

• Magnetic resonance imaging (MRI) and ultrasonography
Treatment of pheos in pregnancy

• Beta blockade (propranolol) should not be used without prior alpha blockade (phenoxybenzamine), because unopposed alpha-adrenergic activity may lead to vasoconstriction and a hypertensive crisis

• Combined alpha and beta blockade is safe in pregnancy
Treatment of pheos in pregnancy

• Surgical intervention should be performed before 24 weeks' gestation, after adequate alpha blockade has been achieved.

• After 24th week treated with alpha and beta blockade from the beginning of the second trimester to term, with good fetal outcomes.
Delivery in pregnancies with pheos

- Delivery with adequate alpha blockade
- Elective cesarean delivery may be performed, followed immediately by adrenal exploration
- Higher maternal mortality rates with vaginal delivery (31%) than with cesarean delivery (19%)