

Adrenal Insufficiency During Pregnancy

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Disclosures

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Outline

- Primary Adrenal Insufficiency
- Physiological changes HPA axis during pregnancy
- Diagnosing AI during pregnancy
- Management of AI during pregnancy
 - Glucocorticoid and mineralocorticoid replacement
 - Stress dosing
- Congenital adrenal hyperplasia
- Cases

Learning Objectives

- Know the normal physiological changes in glucocorticoid and mineralocorticoid that occur during pregnancy
- Describe the presentation of adrenal insufficiency during pregnancy
- Understand the management of glucocorticoid replacement during pregnancy

Primary Adrenal Insufficiency (PAI)

- **Autoimmune (Addison's Disease)**
 - Mostly women 3rd and 4th decade
 - Can be part of polyendocrine syndrome
 - APECED: chronic cutaneous candidiasis, hypoparathyroidism
 - APS type 2: thyroid and type 1 DM
- **Congenital Adrenal Hyperplasia**
 - Most common genetic cause

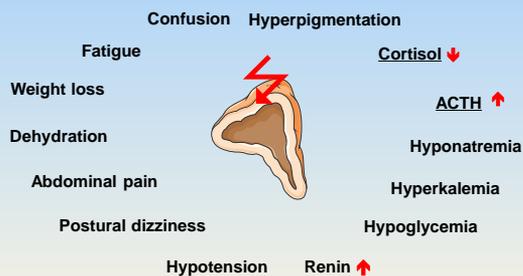
Epidemiology Addison's Disease

Prevalence	~120 cases/million
Incidence	4/million/year

- Up to 90% PAI in adulthood due to autoimmunity in Western countries
- Other causes: infectious diseases (TB), adrenalectomy, neoplasia, genetic causes (more likely to present in childhood)

Bornstein SR *et al.* An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016

Clinical Features PAI: Insidious Onset and Nonspecific Symptoms

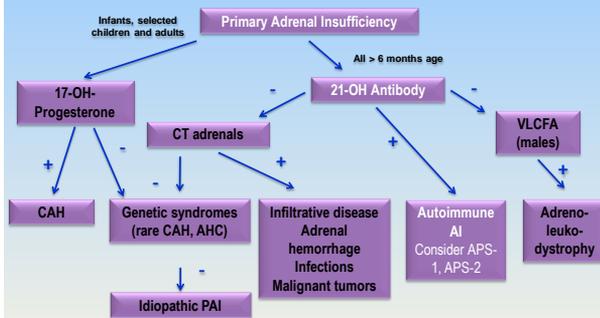


Diagnosing PAI

- **Corticotropin 250µg stimulation test:** cortisol at baseline and after 30 min
 - Peak < 18 µg/dL (500 nmol/L) indicates AI
- **Low basal serum cortisol:** cortisol < 5µg/dl (138 nmol/L). **Elevated plasma ACTH:** >2-fold over UL
- **Measurement of plasma renin, aldosterone, electrolytes**
- **Etiology?**

Bornstein SR *et al.* An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016

Diagnostic Approach to PAI



Bornstein SR et al. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016

Who should be tested and how?

- **Rule out PAI** in any acutely ill patient with clinical symptoms or signs suggestive of PAI
- **Confirmatory testing** with the corticotropin stimulation test if patient's condition and circumstance allows
- **Immediate therapy** with intravenous hydrocortisone (initially 100 mg as bolus followed by a continuous infusion of 200 mg hydrocortisone/ 24hrs) prior to the availability of the results of diagnostic tests in patients with severe AI symptoms or adrenal crisis

Bornstein SR et al. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016

Testing for PAI: Problems and Limitations

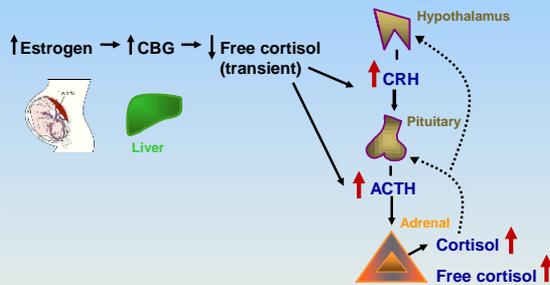
- **High cortisol binding globulin:** Pregnancy and oral contraceptives (estrogens)
- **Low cortisol binding globulin:** Nephrotic syndrome, post-operative, and intensive care medicine
- **Rare situations:** Cortisol binding globulin deficiency, glucocorticoid resistance, and hypersensitivity

Bornstein SR et al. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016

Pregnancy

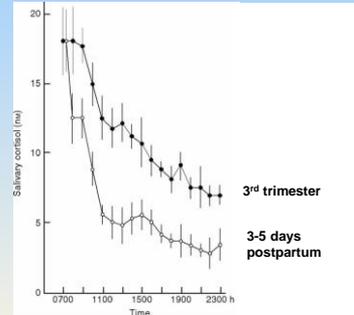
- Symptoms of AI similar to symptoms of normal first trimester of pregnancy (fatigue, nausea, vomiting, hypotension)
- With appropriate treatment, AI patients can have a normal pregnancy and delivery
- Without treatment, adrenal crisis can occur and result in maternal and fetal morbidity and mortality

HPA Axis During Pregnancy



- Progressive increase CRH, ACTH, free cortisol
 - Peaks in 3rd trimester
- ?alterations in set point of HPA axis, placental CRH plays role

Salivary cortisol during normal pregnancy and postpartum



Allolio B et al. *Clinical Endocrinology* 1990

Mineralocorticoid in pregnancy

- Activation of RAAS
- Aldosterone secretion increases → progressive plasma volume expansion
- Progesterone → mineralocorticoid antagonist
 - converted to 17OHP, weaker affinity mineralocorticoid receptor
- Renin release increases by kidney and extra-renal tissues (ovaries, decidua)
- Increase angiotensin II but compensatory mechanisms (i.e. increase prostaglandins) lead to decrease vascular resistance

Adrenal-related hormone levels in pregnant and non-pregnant women

	Concentration in non-pregnant women	Concentration during pregnancy
ACTH	10-60 pg/ml (2.2-13.3 pmol/L)	ACTH increased, but often remains within normal range
Total plasma cortisol	10-25 µg/dL (276-690 nmol/L)	2-to-3-fold elevation
Free plasma cortisol	5-25 µg/dL (140-700 nmol/L)	2-to-4-fold elevation
Salivary cortisol	253 – 717 ng/dL (7-20 nmol/L)	> 2 fold elevation
Plasma renin activity	0.5-3.5 ng/mL/h (6.4-44.8 pmol/L/min)	3-to-7-fold increase
Aldosterone	8-30 ng/dL (221-831 pmol/L)	5-to-7-fold increase in 1st trimester; up to 10-20 fold increase at 38 th week

Monticone S et al. *Nat Rev Endocrinol Suppl* 2012

Maternal and Fetal Risk

- Difficult to diagnose AI in pregnancy, similar to symptoms of normal pregnancy (fatigue, dizziness, nausea, vomiting, abdominal pain, hypotension, syncope)
- Clinical features + hyponatremia, hypoglycemia and salt craving should raise suspicion of AI
- Untreated AI in pregnancy can result in adrenal crisis
- IUGR, low birth weight, oligohydramnios, and intrauterine death reported in untreated AI during pregnancy
- Careful treatment of AI during pregnancy can result in successful pregnancy outcomes

Diagnosis

- Diagnosis of AI in pregnancy requires a high degree of clinical suspicion
- Cortisol values 60-80% higher compared to non-pregnant patients → revised cut offs

Gestational Age	AM Cortisol ($\mu\text{g/dL}$) (nmol/l)	ACTH Stimulation* Peak Cortisol ($\mu\text{g/dL}$) (nmol/l)
1 st trimester	11 (300)	25 (700)
2 nd trimester	16.3 (450)	29 (800)
3 rd trimester	22 (600)	32 (900)

* 250 mcg cosyntropin test (class C drug)

Lebbe M and Art W. *Clinical Endocrinology* 2013

Insulin tolerance test

- What about the ITT in pregnancy?
- Though it's the gold standard for diagnosing AI, it should not be used in pregnancy due to risks of hypoglycemia to the fetus

Glucocorticoid Treatment

- GOAL: glucocorticoid replacement dose to ensure maternal and fetal health
- Hydrocortisone is treatment of choice
 - efficiently inactivated in placenta by 11B-HSD type 2 (does not reach fetus)
 - cortisone acetate, prednisolone, or prednisone can also be used
- recommend against using dexamethasone because it is not inactivated in the placenta
- 20-40% increase in hydrocortisone dosing during the third trimester (5-10mg)

Management

- Glucocorticoid dosing is based on clinical signs and symptoms (weight change, fatigue, postural hypotension or hypertension, hyperglycemia)
- Evaluated at least once per trimester
- Under-replacement → risk of adrenal crisis
- Over-replacement → risk of gestational diabetes

Mineralocorticoid Treatment

- Mineralocorticoid requirements are difficult to assess due to overlap with symptoms of normal pregnancy
- PRA increases during pregnancy and cannot be used to monitor
- Typically no change is made in fludrocortisone dose but follow clinically (salt craving, orthostatic symptoms)
- Salt supplementation can be used

Adrenal Crisis Prevention

- Stress doses (double or triple dose) for fever, GI illness, outpatient procedures
- Hydrocortisone injection 100 mg im for persistent vomiting
- Home supply of emergency injection kit
 - Self-injection teaching
- Education!

Stress Dosing

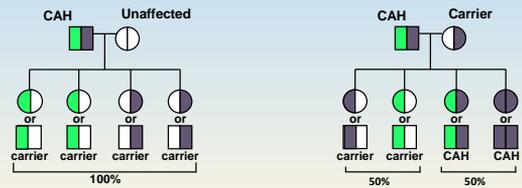
- Stress doses GC needed during active labor and for delivery
 - Doses used for major surgical stress should be initiated at onset of active labor (cervix dilation > 4 cm and/or contractions every 5 minutes for > 1 hour)
 - Hydrocortisone bolus 100 mg iv followed by continuous infusion of 200 mg/24 hours (OR 50 mg every 6 hours iv or im)
- After delivery, GC dose can be tapered rapidly (within 3 days) to pre-pregnancy dose

Pregnant CAH Patient

- Biomarkers 17OHP, androstenedione increase with pregnancy and cannot be used to monitor
- follow free testosterone (every 2 months). Mild elevations do not affect fetus
- Increase GC dose (20-40%) especially in 24th week of gestation and onward to reflect physiologic increase of cortisol
- Do not use dexamethasone

CAH is autosomal recessive

- Genetic counseling and carrier status of partner recommended
- If Carrier status of partner unknown: chance classic patient will have child with classic CAH is 1 in 120



Nonclassic CAH

- Presentation during childhood: early (< 8 yo girls, < 9 yo boys) pubic hair (pubarche), rapid growth with advanced bone age
- Adult women: hirsutism, oligomenorrhea, acne, infertility
- Adult men: asymptomatic

Speiser et al. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2010

When to Treat Nonclassic CAH

- Subset of children
- Adult women: infertility
 - Subfertility common in NC CAH women
 - Rate miscarriages decreased with GC therapy: 26% vs. 6.5%
Bidet M et al. *J Clin Endocrinol Metab* 2010; ;95:1182-90
- GC treatment not required for fertility
 - 68% of 203 pregnancies among 101 NC CAH women occurred prior to diagnosis
Moran C. *J Clin Endocrinol Metab* 2006
- Genetic counseling important
 - 2/3 NC pts carry classic gene

Speiser et al. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2010

Pregnant NC CAH Patient

- No need to follow biomarkers CAH. Androgens not high enough to effect fetus
- Typical GC dose lower than classic patient
 - Prednisone 2 mg twice daily commonly used
 - Usually no need to increase dose last trimester
- Do not use dexamethasone
- Stress dosing during labor and delivery if receiving GC therapy

Summary

- Majority of pregnant women with PAI have established diagnosis prior to conception BUT significant clinical consequences if diagnosis missed
- Diagnostic testing needs to account for normal pregnancy-related endocrine changes
- Increase GC dose typically needed
- Stress dosing during labor and delivery similar to major surgical stress

CASES