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

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>~120 cases/million</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>~4/million/year</td>
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- 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)

Clinical Features PAI: Insidious Onset and Nonspecific Symptoms

- Confusion
- Hyperpigmentation
- Fatigue
- Weight loss
- Dehydration
- Abdominal pain
- Postural dizziness
- Hypotension
- Renin
- Cortisol

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?

Diagnostic Approach to PAI

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

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

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

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

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>AM Cortisol (µg/dL) (nmol/l)</th>
<th>ACTH Stimulation* Peak Cortisol (µg/dL) (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td>11 (300)</td>
<td>25 (700)</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>16.3 (450)</td>
<td>29 (800)</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>22 (600)</td>
<td>32 (900)</td>
</tr>
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</table>

* 250 mcg cosyntropin test (class C drug)

Lebbe M and Arlt 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, prenisolone, 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
Why are many women with classic CAH not interested in fertility?

- Androgen effects on developing brain?
- Genital ambiguity/surgical complications
  - Vaginal stenosis common
  - Psychological impact, poor self-esteem, dissatisfaction with sex life
- Most women with CAH report heterosexual orientation, but the frequency of homosexuality or bisexuality is increased

CAH and pregnancy

- Infertility: progesterone/androgen levels, sexuality concerns, and difficulty with endometrial implantation
- Today: women with classic CAH having normal pregnancies and delivering healthy infants if hormone levels well controlled
- Pregnancy rate for classic women trying to conceive has been reported as normal (91.3% in UK study) Casteras A et al. Clin Endocrinol 2009
**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

**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%
  - 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 2008
- Genetic counseling important
  - 2/3 NC pts carry classic gene

**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