Adrenal and pituitary disease in pregnancy

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Academic half day
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Disclosure

- Relevant relationships with commercial entities:
  - None
- Potential for conflicts within this presentation:
  - None
- Steps taken to review and mitigate potential bias:
  - N/A

2/10/17

Objectives

By the end of this talk, you should know:

1. Basic maternal-fetal normal physiology of HPA axis.
2. How our approach to pituitary and adrenal diseases differs in the pregnant patient.

Overview

- Adrenal
  - Cushing's syndrome
  - Addison's
  - CAH
  - Chronic CG Rx
  - Hyperaldo
  - Pheochromocytoma
- Pituitary:
  - Prolactinoma
  - Acromegaly
  - Hypopituitarism

Overview

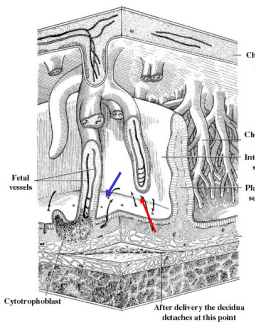
- Adrenal
  - Cushing's syndrome
  - Addison's
  - CAH
  - Chronic CG Rx
  - Hyperaldo
  - Pheochromocytoma
- Pituitary:
  - Prolactinoma
  - Acromegaly
  - Hypopituitarism

Mom

Placenta

Fetus

Cross-section of placenta



Fetus

Syncytiotrophoblastic covering

Mother

https://www.youtube.com/watch?v=bped-RVWsLk

ADRENAL

Adrenal physiology in pregnancy

- Placenta makes estrogen and progesterone (no other steroid hormones)
- Needs DHEAS as substrate
- DHEAS comes from the fetus
- Fetal adrenal glands are large, produce 5X as much steroid hormones as adult does
- Fetal steroids affect lung maturation and initiation of labour

Adrenal physiology: Cortisol

- ↑Estrogen → ↑CBG
  - ∴ Total cortisol levels are increased
- ↑ Free cortisol, too (↓ clearance)
- Very little of maternal steroid hormones are seen by fetus:
  - placenta converts cortisol to cortisone
  - placenta delivers GC back to maternal circulation
  - placenta aromatizes maternal androgens to estrogen
  - dexamethasone is delivered to the fetus

Adrenal physiology cont'd

- Placenta produces ACTH and CRH
- Maternal levels of ACTH
  - T1: ↓ slight
  - T2: normal
  - T3: ↑ slight

Cushing syndrome

Lindsay, Endocr rev 2005
Polli Pituitary 2004

- Rare (< 100 cases) reported in literature (75% infertile)

New diagnosis:

- Usually ADRENAL source in pregnancy
  - 60% adrenal, ¾ benign
- Maternal risk: GDM (1/3), ↑BP 70%,
  - ↑ preeclampsia, CHF, death
- Fetal risk:
  - Spontaneous abortion, preterm delivery
  - 15% perinatal mortality
  - Rarely suppression of the HPA axis

Cushing syndrome: Challenges in diagnosis

- In normal pregnancy:
  - 8 AM plasma cortisol: 420 ± 110 nmol/l at 11 weeks of gestation and 980 ± 250 nmol/l at 26 weeks of gestation; the levels remained elevated until labor and delivery
  - 24 hr UFC: ↑2-3X by T2 and T3
  - O/N DST inaccurate since:
    - ↑CBG
    - Resistance to suppression (CRH + ACTH made in placenta)
    - Can use higher cutoff for diagnosis
  - Maintained circadian rhythm

Cushing syndrome: Challenges in diagnosis (cont'd)

- For diagnosis:
  - 24 hour UFC > 3X elevation
  - 8 mg O/N DST: similar to non-pregnant state
  - ACTH level to establish if ACTH-dependent: (often not fully suppressed in ACTH-independent Cushings)
- Imaging: US or MRI

Cushing's syndrome: Treatment

- Early T2 surgery: 6/7 fetuses survived with no deficit vs 7/19 with no OR
- GC after OR, start wean after delivery
- Ketoconazole has been used (3 cases reported)
  - Teratogenic in animal studies
- Metyrapone has been used

Addison's disease

Ambrosi J Endo Invest 2003

- If undiagnosed hypoadrenalism:
  - Fetal IUGR
  - Low maternal BP, skin hyperpigmentation
  - Addisonian crisis during delivery

Addison's Dx and Rx

- Diagnosis: Cortrosyn stim test (but no established ref values in pregnancy)
  - R/O associated diseases (thyroid, pituitary)
- Treatment:
  - Usual GC and MC replacement are continued throughout pregnancy
  - T1: May need dexamethasone im 1-2 mg/d with severe nausea and vomiting
  - T3: May require slightly higher doses of GC and florinef

CAH: 21-OH deficiency

Lo JCEM 1999, Endo Metab Clin N Am 2001
Meyer-Bahlburg Arch Sex Behav 2008

- Woman may have difficulty conceiving
  - Hyperandrogenism, abn introitus, less interest?
- Issues for fetus
  - Androgenization from maternal androgens (limited, but can happen)
  - CAH if father carries defective gene (1/62 general population, CYP21 genotype)
  - HPA suppression due to maternal excess GC, especially if dexamethasome used
  - Delivery with android pelvis

CAH: 21-OH deficiency

- Use GC *OTHER THAN* dexamethasone, unless concerned about possible fetal CAH
- Assess clinical status, electrolytes, serum androgens q 6 weeks T1, then q 8 weeks
  - Target testosterone/free testosterone levels: high normal range for pregnancy
- Fetal sex determination (less concern re: maternal androgens for male fetus)

CAH: Delivery

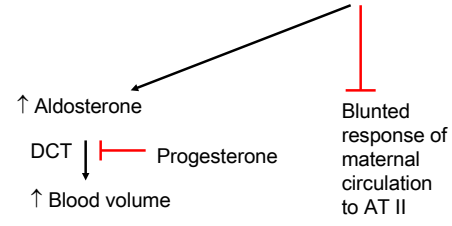
- Stress dose steroids for delivery (solucortef 50-100 mg iv q 8 hr) then rapid taper to previous maintenance dose
- May need C-section for android pelvis/reconstructed genitals
- Evaluate infant for ambiguous genitalia
  - Ambiguous genitalia could be due to CAH in fetus or from maternal androgens crossing placenta

Patients on chronic GC therapy

- No adverse effect on fetus
- Dexamethasone should NOT be used
- Screen mother for GDM, hypertension
- Stress dose steroids for delivery
- Should not affect fetus (monitor for theoretical HPA axis suppression)
- GC therapy safe in breastfeeding

Renin-angiotensin-aldosterone system

↑ E+P → 4X ↑ renin → ↑ AT II



Hyperaldosteronism

Abraham eMedicine 2007

- Rare in pregnancy (18 cases reported)
- Normal pregnancy:
  - ↑ plasma aldosterone levels
  - ↑ renin levels are increased in normal pregnancy, will be lower in primary hyperaldosteronism

Primary Hyperaldosteronism: Dx + Rx

- Diagnosis:
  - Dangerous to salt load
  - Dynamic testing: renin won't ↑ in response to upright posture in primary hyperaldo
- Treatment:
  - OR in T2
  - Antihypertensives: methyldopa, β-blockers, calcium channel blockers

Pheochromocytoma

Abraham eMedicine 2007

- Patient presents similar to the non-pregnant state
- High mortality if unrecognized (up to 48% mother, 54% fetus)
- If treated: 2% maternal mortality, fetal 11%

Pheochromocytoma: Dx + Rx

- Diagnosis:
  - Urinary catecholamines and metanephrines not altered by pregnant state
  - Localize with US/MRI
- Medical treatment:
  - Phenoxybenzamine +/- propranolol
  - Labetolol
- Surgery:
  - Before 24 weeks after α-blockade
  - After 24 weeks: after fetal maturity with C-section

PITUITARY

- Mass effect
- Hyperfunction
- Hypofunction

Pituitary size in pregnancy

Gonzalez Am J Med 1988

- Gradual ↑ of 30% in maternal pituitary volume over gestation
- 12 mm in height a few days postpartum (↑2.6 mm)
- Rarely causes visual field defects
- No ↑ pituitary tumor formation during pregnancy

Prolactin in pregnancy

Mom:

- Estrogen→ ↑Lactotrophs (20% →50% of pituitary cells)
- ↑Prolactin:
  - T1 20-40
  - T2: 50-150
  - T3: 100-400
- Prolactin is non-glycosylated (more active)

Placenta produces prolactin (into amniotic fluid)

Fetal prolactin: 80-500

Prolactinomas in pregnancy

- Getting pregnant
  - Assess safety: tumor size, hypopituitarism
  - 90% pregnancy rate with DA treatment
  - Switch to bromocriptine if possible
  - Barrier contraception to establish cycle dates
  - GnRH has been used for DA failure
    - Molitch J Reprod Med 1999

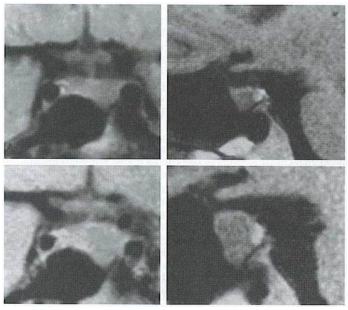
Prolactinomas

- STOP bromocriptine once pregnant
  - unless tumor > 10 mm (Molitch, J Reprod Med 99)
- Monitoring in pregnancy q 2 months
  - Headache
  - Visual field:
    - Formal with macroadenomas
  - DI, other hormone deficiencies
  - MRI only if problem with above
  - NOT prolactin levels

Effects of pregnancy on tumor:

- Risk of growth off therapy (Molitch, 92)
  - Micro: 1.3%
  - Macro:
    - Untreated = 25%
    - After shrinkage with DA = "less likely"
    - After surgery = 3%
- Another series (Seshadri, 07)
  - Micro (104 patients): none significantly regrew
  - Idiopathic (85 patients): none
  - Macro (21 patients), off bromocriptine: 2
- After pregnancy:
  - Breast feeding is safe
  - Often regression of tumor!

Prolactinoma growing in pregnancy



Therapy of prolactinoma in pregnancy

- If tumor growth occurs:
  - Bromocriptine (cabergoline)
  - Surgery
- Risk of medications (Ricci Reprod Toxicol 2002):
  - Bromocriptine: FU for >6000 pregnancies (kids followed up to 9 years)
  - Cabergoline: FU for 265 pregnancies
- No info for quinagolide

Box 5: Management of hyperprolactinemia in pregnancy

- There is no evidence of increased teratogenicity associated with bromocriptine or cabergoline use during pregnancy[13,16]
- Similarly, there is no evidence of increased risk of abortion or multiple pregnancies with dopamine agonist use
- If the tumour size before pregnancy is < 10 mm, dopamine agonist therapy is stopped during pregnancy because the risk of tumour expansion is low[13]
- If the tumour size before pregnancy is ≥ 10 mm before pregnancy, bromocriptine use is advised during pregnancy to avoid significant tumour expansion[15]
- All patients should be evaluated every 2 months during pregnancy
- Formal visual field testing is indicated in patients with symptoms or a history of macroadenoma
- If visual field defects develop despite dopamine agonist treatment, early delivery or pituitary surgery should be considered[17]

Serri, O. et al. CMAJ 2003;169:575-581

CMAJ·JAMC

Growth hormone in pregnancy

- Mom:
  - ↓ somatotroph number
  - ↓ GH by T2
  - ↑ IGF-1 (due to stimulation by fetal GH)
- Fetus:
  - Makes GH
  - Makes IGF-1 and IGF-2 (may be independent of GH)
- Placenta:
  - Variant GH
  - GHRH, IGF-1

Acromegaly in pregnancy

- Getting pregnant
  - Often irregular menses or amenorrhea
  - May be due to ↑prolactin or gonadotroph destruction or stalk effect on gonadotrophs
  - May need to use bromocriptine to conceive
- Diagnosing acromegaly during pregnancy
  - Challenging (↑GH from placenta)
  - Pulsatile GH, MRI

Acromegaly (cont'd)

- Monitoring during pregnancy
  - Mass effect
  - Hyperfunction: Insulin resistance, cardiac
  - Hypofunction
- Treatment during pregnancy: If mass effect
  - Bromocriptine
  - There are reports of octreotide being used (crosses placenta)
  - Surgery

Hypopituitarism

During pregnancy:

- Due to pre-existing mass lesion
- Vasopressinase from placenta: ADH↓
- New onset diabetes insipidus during pregnancy may be associated with acute fatty liver of pregnancy and the HELLP syndrome

Postpartum:

- Due to Sheehan's syndrome
- Due to hypophysitis

Treatment of hypopituitarism

Thyroxine	↑ Dose (30-50%) in T1: Aim free T4 high-normal (Alexander NEJM 04)
Cortisol	Not dexamethasone
ADH	Vasopressinase ↑ risk DI Treat with DDAVP
Sex hormones	No need
GH	No need
Prolactin	Can't breast feed
Oxytocin	No effect

What do I need to know?

1. Bromocriptine can be useful:
   - To treat prolactinoma
   - To treat acromegaly
   - To rescue mass effect of pituitary tumors during pregnancy by shrinking the normal expanded pregnant gland.
2. Most patients with prolactinomas and GH-producing tumors do well.
3. If you use a non-dex glucocorticoid to replace cortisol deficiency, the risk of fetal HPA axis suppression is small.

What do I need to know? (cont')

4. Cushing's syndrome and acromegaly are very difficult to diagnose during pregnancy, due to effects of fetal and placental physiology (important to understand those effects).
5. Cushing's syndrome and pheochromocytomas are BIG trouble in pregnancy.
6. Vasopressinase can precipitate otherwise mild preclinical DI.