27 Year-Old Pregnant Woman with CAH

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8/30/2012

HPI

- 27 yo woman 14 weeks pregnant with hx of CAH referred by OB for further evaluation
- Diagnosed with classic CAH at birth (21-OHD); genetic testing revealed gene sequencing 30 kb deletion of CYP21A2 and one rare mutation p.445X)
- Was followed by an outside Endocrinologist in the past, but was referred to Endo clinic at U of C after initial OB visit here.
- Never used contraception because she was told getting pregnant would be difficult
- Pregnancy was not planned; but she considers this baby a miracle
- An Outside Endocrinologist advised her to terminate the pregnancy prior to even knowing the sex of the baby; Patient has had no hormone levels checked prior to current visit

HPI

- Currently taking hydrocortisone 10 mg po q8am, 10 mg q3pm, and 15 mg q9pm
- Also taking florinef 0.1 mg po qam and 0.05 mg qpm
- Born with ambiguous genitalia at birth
- Has had multiple reconstructive vaginal surgeries in 2003-4 due to vaginal agenesis and displaced urethra
- Has mild acne and hirsutism (denies worsening with pregnancy)
- Also has deep voice; gained 2-3 lbs with pregnancy

Past Medical History

- Congenital Adrenal Hyperplasia
- Multiple Vaginal Reconstructive Surgeries in 2003-4 due to vaginal agenesis and displaced urethra
- Chronic lymphedema of the lower extremity due to vaginal reconstruction surgery in 2003 requiring skin graft
- Depression

Family Hx, Social Hx, Meds

Family Hx:

Adopted-does not know family history

Social Hx: single

Lives with her adopted mother who is supporting her through current pregnancy

Former smoker, quit in 2011

Denies alcohol, illicit drugs

Medications:

-Cymbalta 60 mg po daily
-Florinef 0.1 mg qam 0.05 mg qpm
-Hydrocortisone 10 mg q8am,
10 mg q3pm, and 15 mg qpm

Physical Exam

- VS: BP 100/60 Pulse 84 Height: 5' 3.5'' Weight- 84.64 kg, BMI 32.5 kg/m^2
- Gen: well-appearing (non-cushingoid appearing), no acute distress, has deep voice
- HEENT: NCAT, oropharynx clear
- Neck: no thyromegaly
- Respiratory: CTA b/l
- CVS: +S1/S2, no murmurs
- Abdomen: soft, gravid, nontender, +bs
- Extremities: chronic lymphedema of LE
- Skin: mild acne, no hair loss or receding hairline, Ferriman-Gallwey score: 1 chin, 1 upper lip, 1 lower abdomen, zero everywhere else. No violaceous striae
- GYN exam (per OB): "could not tolerate pelvic speculum exam with pediatric speculum"
- Neuro: Alert and oriented x 3, proximal muscle strength normal

LABS:

135 | 105 | 9 / 100 9.8\ 14 / 195

3.2 | 20 |0.7 \ /40.7 \

HbA1c- 5.1%

DHEA-SO4 <15 (65-380 ug/dl)

ACTH 29.1 (<52 pg/ml)

Total testosterone 70 (20-60 ng/dl)

Te Binding Globulin 210 (20-100 nmol/L)

Calculated free testosterone 5 (3-9 pg/ml)

Androstenedione 168 (30-200 ng/dl)

Congenital Adrenal Hyperplasia (CAH)

- Most common enzyme deficiency that accounts for more than 90% of cases is 21-hydroxylase deficiency
- Next common form is 11Β-hydroxylase deficiency, followed by 3Β hydroxysteroid dehydrogenase deficiency, and then exceedingly rare forms
- Females with Classical 21-OHD, 11-Β hydroxylase D, 3-Β OHD generally present at birth with virilization of their genitalia
- Three expressions of 21-OHD have been identified: 1.) classic simple virilizing with manifestions of excess androgen secretion 2.) classic salt wasting, which consists of aldosterone deficiency in addition to excess androgen secretions due to the 21-OHD defect in the parallel mineralocorticoid pathway in the zona glomerulosa. 3.) Nonclassic-less severe hyperandrogenic, variably expressed and allelically distinct form, in which affected males and females have unambiguous genitalia at birth

CAH

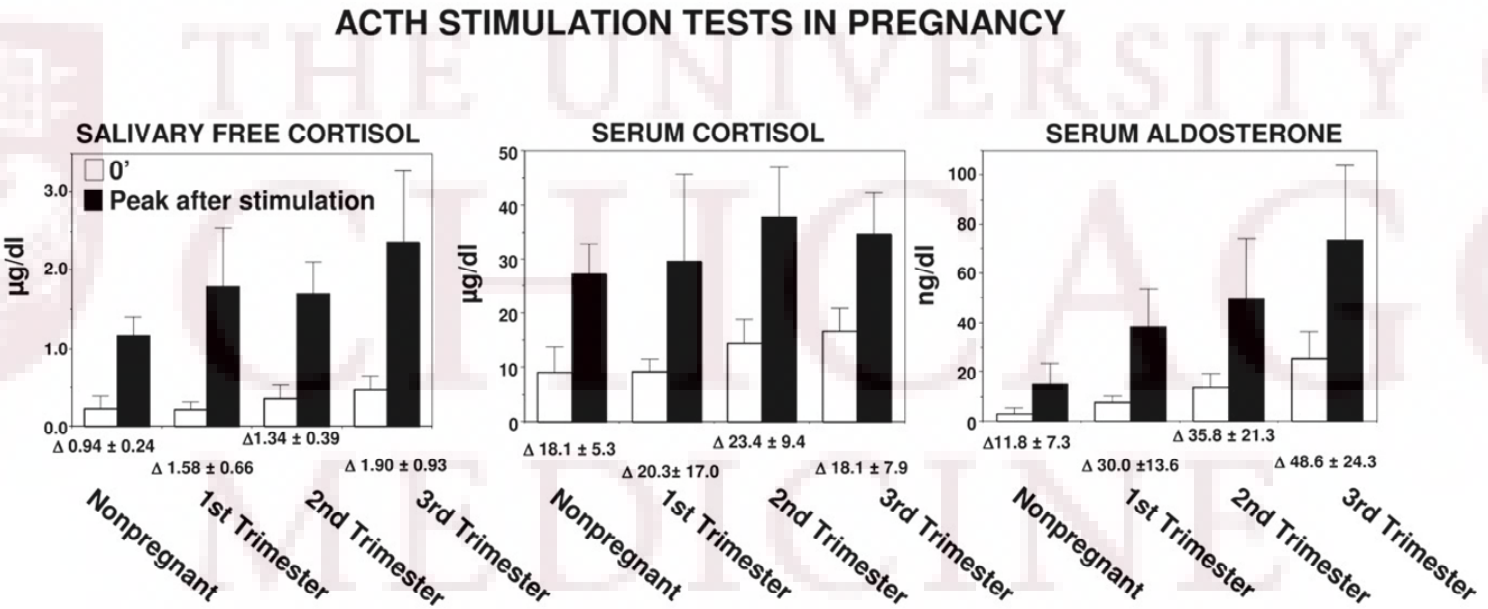
- Adrenocortical function begins at 7th week of gestation; female fetus with classical CAH is exposed to adrenal androgens at sexual differentiation (9-15 weeks age)
- Androgens interact with the receptors on genital skin leading to clitoral enlargement, fusion and scrotalization of labial folds, failure of labial rotation, and placement of the clitorus in the male position
- Although differentiation of male genitalia is not affected, high testosterone levels of adrenal origin cause gonadotropin suppression, which result in the characteristic finding in older boys of a large penis and small testes
- Hyperpigmentation of the genitalia in both males and females can result from high ACTH secretion.

CAH and Fertility

- Although females with Classical CAH maintain the internal genitalia potential for fertility (Uterus, fallopian tubes, ovaries develop normally), fertility is reduced.
- Meyer-Bahlburg compared the fertility of women with different forms of classic CAH (21-OHD). In these women with adequate introitus and sexual activity, he found that fertility was ~60% with the simiple virilizing form (n=25), whereas fertility was only 7% in the salt-wasting form (n=15)
- Most widely recognized cause of low fertility among CAH women is due to inadequate control of adrenal hormones (ovulatory failure secondary to steroidal excess)
- Adequate biochemical control is assessed by measuring serum levels of 17-OHP, androstenedione, and testosterone (measured 2 hours after morning corticosteroid)
- Titration of dose aimed at maintaining androgen levels within normal range of women and 17-OHP levels <1000 ng/dl

Adrenal Reserve in Pregnancy

Mean SaFC, mean SC, and mean serum aldosterone concentrations before (0 min) and after (peak cortisol) iv administration of 250 μg ACTH. The data were measured in first-trimester (n = 4), second-trimester (n = 16), or third-trimester (n = 16) healthy pregna...



Suri D et al. JCEM 2006;91:3866-3872

The Journal of Clinical Endocrinology & Metabolism

CAH and Pregnancy

- Hydrocortisone is the preferred treatment of pregnant women affected with CAH because unlike dexamethasone, it is metabolized by the placental enzyme 11ß-HSD 2 and does not affect the fetus
- Prednisone and prednisolone also cross the placenta, although in smaller concentrations than dexamethasone.
- 17-OHP and androgens should be checked every trimester
- For labor and delivery, stress doses of hydrocortisone should be administered

Prenatal Treatment for Fetus

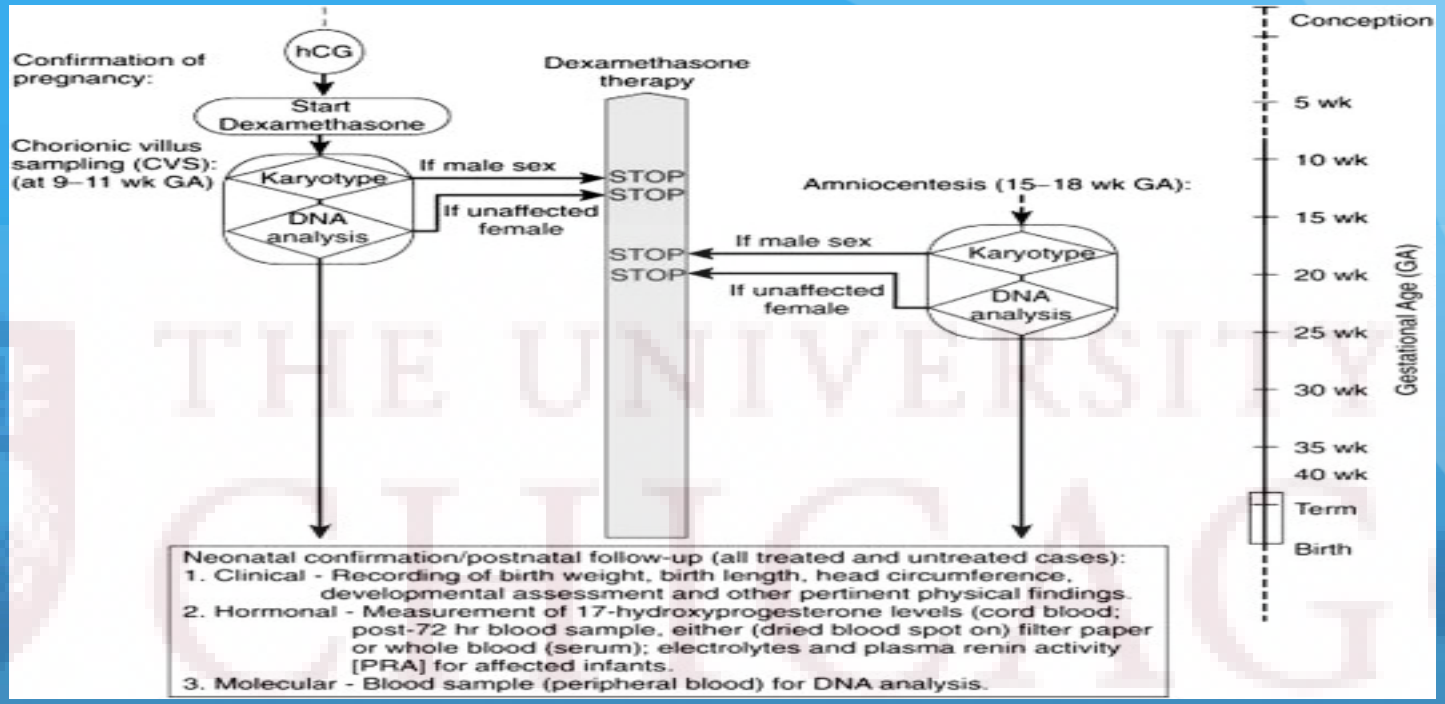


Fig.?3 Algorithm of treatment, diagnosis and decision-making for prenatal treatment of fetuses at risk for 21-hydroxylase deficiency congenital adrenal hyperplasia.<ce:cross-ref refid="bib102"> <ce:sup loc="post"> 102</ce:sup> </ce:cross-ref> Pe...

Oksana Lekarev , Maria I. New

Adrenal disease in pregnancy

Best Practice & Research Clinical Endocrinology & Metabolism Volume 25, Issue 6 2011 959 - 973

http://dx.doi.org/10.1016/j.beem.2011.08.004

Our Recommendations

- Goal throughout pregnancy is to keep androgen levels normal and 17-OHP<1000 ng/dl
- Continue hydrocortisone and florinef, but requirements may increase as pregnancy progresses.
- Androgen levels need to be checked every trimester and dosing of hydrocortisone and florinef may need to be adjusted. Ordered 17-OHP since it was not checked with previous labs.
- Blood pressure and electrolytes will need to be closely monitored.
- Recommend genetics consult.

Genetics Consult Recs

- Carrier testing of the CYP21A2 gene was done for patient's husband (father of fetus) to determine if he was a carrier of CAH
- He tested negative for both common and rare mutations.
- Genetics counselor gave option for amniocentesis for determination of fetal sex but did not feel it was necessarily indicated for this particular case since the chance the fetus could be affected was extremely low.

Recent Update

- Patient had complete anatomy screen at 20 weeks which revealed the fetus had normal male external genitalia and normal fetal anatomy.
- Has upcoming appointment in Endo clinic with Dr. Flynn to follow androgen levels

Take Home Points

- 1.) Hydrocortisone is the preferred treatment of pregnant women affected with CAH because unlike dexamethasone, it is metabolized by the placental enzyme 11ß-HSD 2 and does not affect the fetus.
- 2.) 17-OHP and androgens should be checked every trimester in pregnancy (goal to keep androgen levels normal and 17-OHP levels <1000 ng/dl).
- 3.) Dexamethasone treatment should be initiated early in all high-risk pregnancies and maintained until confirmation is obtained that treatment is not necessary (genetic male or unaffected female).

References

- 1.) Lekarev O and New MI. *Adrenal disease in pregnancy.* Best Pract Res Clin Endocrinol Metab. 2011 Dec;25(6):959-73.
- 2.) Wanjrajch, M.P. and New MI. *Chapter 103: Defects of Adrenal Steroidogensis.* Volume II. Endocrinology: Adult and Pediatric. J. Larry Jameson and Leslie J. DeGroot. 6th edition. 2010.
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- 4.) Daesman Suri, Jill Moran, Judith U. Hibbard, Kristen Kasza, and Roy E. Weiss. *Assessment of Adrenal Reserve in Pregnancy: Defining the Normal Response to the Adrenocorticotropin Stimulation Test. The Journal of Clinical Endocrinology & Metabolism October 1, 2006 vol. 91 no. 10 3866-3872.*