

# Consensus Statement on Treatment of 21-Hydroxylase Deficiency

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## 1. Clinical Evaluation

Endocrinology consult if:

- Clinical suspicion of CAH
- Infant with ambiguous genitalia
- Abnormal newborn screening result (high 17-OH Progesterone for age)
- Complete history and physical exam – check for maternal virilism
- Ultrasound exam of internal genitalia and adrenal glands
- Karyotype or FISH for sex chromosome material
- Serial 17-OH Progesterone levels in premature babies

## 2. Newborn Screening

- Detects classical CAH and some cases of nonclassical CAH
- Sample ideally obtained at 48-72 hours of age
- Positive result requires validation with second test
  - Serum/plasma 17-OH progesterone
  - Urine steroid profile
  - ± CYP21 gene analysis
- Confirm salt wasting status with:
  - Serial serum/plasma and urine electrolytes
  - Plasma renin activity or direct renin
  - ± CYP 21 gene analysis

## 3. Prenatal Diagnosis and Treatment

- Treatment effective if started by 9 weeks after mother's LMP
- No adverse effects to fetus reported (although some theoretical concerns)
- Mothers have edema, striae, weight gain, but no diabetes or hypertension
- Only 1 of 8 fetuses will continue treatment to end of pregnancy (6 unaffected, 1 male will not need therapy)
- Inclusion criteria:
  - 1) previously affected sib or first degree relative with known mutations causing classical CAH, proven by DNA analysis
  - 2) reasonable expectation that father is same as the proband's
  - 3) availability of genetic analysis
  - 4) therapy starts before 9 weeks after mother's LMP
  - 5) no plans for abortion
  - 6) reasonable expectation of adherence to regimen
- Optimal dose of dexamethasone is 20 ug/kg/day divided t.i.d.
- Monitor maternal BP, urine glucose, HbA1c, weight, plasma cortisol, DHEA-S, and androstenedione at start and q 2 months
- Measure urine estriol after 15-20 weeks gestation.
- Treatment should only be undertaken after full discussion. This is NOT standard of care in the community.
- Written consent MUST be obtained. Preferably done under supervision of IRB and in context of a study

## 4. Surgical Management

Decision should be made by parents

Goals of surgery are:

- 1) genital appearance compatible with gender
- 2) unobstructed urinary emptying without incontinence or infections
- 3) good adult sexual and reproductive function

Once decision made to raise child as female:

- If high proximal junction between vagina and urethra
  - Best time is 2-6 months of age (technically easier than at later times)
  - Experienced surgeon
- If junction between vagina and urethra is near perineum

Surgery may not be necessary  
Anatomical studies required to make best decision  
Clitoroplasty may not be necessary  
If clitoroplasty is performed, must preserve neurovascular bundle, glans, preputial skin related to the glans  
If surgery done early, should be one-stage repair using newest techniques of vaginoplasty, clitoral, and labial surgery at a center with at least 3-4 cases per year. (designated surgical team)  
Revision vaginoplasty often required at adolescence  
Surgery between 12 months of age and adolescence not recommended in the absence of complications causing medical problems  
Vaginal dilation before adolescence contraindicated  
Minimize genital exams and photographs to those that are necessary  
For virilized 46 X,X patients with late presentation, consider sex re-assignment only after psychological evaluation of patient and family and period of endocrine replacement therapy

## 5. Psychological Issues

Females with CAH show behavioral masculinization

- Most pronounced in gender role behavior
- Less so in sexual orientation
- Rarely in gender identity

Must consider societal setting when making decision about sex assignment/re-assignment

## 6. Treatment Considerations

Goals are:

- Replace deficient steroids
- Minimize sex steroid and glucocorticoid excess
- Prevent virilization
- Optimize growth
- Protect potential fertility

### *Glucocorticoid Use*

Typical dose of hydrocortisone is 10-15 mg/m<sup>2</sup>/day divided t.i.d.  
Especially in infancy, doses may need to be higher (25 mg/m<sup>2</sup>/day)  
Crushed hydrocortisone tablets preferred to oral suspension  
Complete adrenal suppression causes Cushingoid features, obesity and poor linear growth  
When growth is complete, longer acting steroids may be used  
Prednisolone at 2-4 mg/m<sup>2</sup>/day divided bid is preferred  
Dexamethasone can be given at 0.25-0.375 mg once daily  
GnRH agonist may be required for central precocious puberty

### *Mineralocorticoid Use*

All classical CAH patients should receive fludrocortisone at diagnosis (0.05-0.30 mg/day)  
Sodium chloride supplements often needed in infants (1-3 g/day = 17-51 mEq/day) divided in several feedings  
Need for continuing therapy based on measures of blood pressure and renin

### *Diagnosis and Treatment of Nonclassical CAH*

Diagnostic test is 60 minute ACTH test [250 ug (1-24)ACTH IV bolus]  
Morning serum 17 OH Progesterone can be used as a screening tool  
Treat only if symptomatic (bone age and poor height prediction, hirsutism, severe acne, menstrual irregularities, testicular masses, infertility)

### *Monitoring Treatment of Classical CAH*

Physical Findings

- Growth rate
- Cushingoid features
- Blood pressure

Laboratory (not all are necessary)

- Serum/plasma electrolytes
- 17 OH Progesterone
- Androstenedione
- Testosterone
- Plasma renin activity or direct renin

Measure labs q 3 months during infancy and then q 4-12 months thereafter  
Patients receiving adequate hormone therapy may have lab values above the normal range

### Stress Dosing

Carry and wear medical ID

Need emergency supply of IM hydrocortisone or glucocorticoid suppositories

Give 2-3 times normal glucocorticoid dose for stress related to:

- Fever >38.5°C

- Vomiting

- Anorexia

- Trauma

- Pre-operatively

- ±Endurance sports

Parenteral steroids needed if:

- Vomiting

- Unable to take oral steroid

- Trauma

- Surgery

### Stress IV hydrocortisone doses

Age	Initial Dose	Subsequent Dose
< 3 yr	25 mg	25-30 mg/day
3-12 yr	50 mg	50-60 mg/day
>12 yr	100 mg	100 mg/day

May need IV glucose and sodium chloride

### *Management in adolescence*

Perform genital exam only if there is a clinical or laboratory indication:

- Poor control of sex steroid production

- Pubertal progress

- Clitoral size

- Counseling about use of tampons or sexual activity

Explain reason to patient and family for doing genital exam

### Psychological Well Being

Assess need for counseling routinely

Offer sex- and age-appropriate counseling, regarding sexual function, future surgery, gender role, issues related to living with a chronic disease

### *Care During Transition to Adulthood*

Transition team include endocrinologists, gynecologist, urologist, psychologist with specific expertise

Males should be counseled that treatment improves fertility and reduces risk of palpable testicular masses

Periodic exams, ultrasound and MRI to assess extent of testicular masses.

Surgical removal of a glucocorticoid unresponsive mass may preserve or improve fertility

Women need assessment of genital repair and counseling if sexual dysfunction is concern

Women with nonclassical CAH should be counseled about risk of infertility (actual risk unknown)

### *Management of a Pregnant Woman with CAH*

- Require tertiary care

- Treat with Prednisone or Hydrocortisone (do not cross placenta)

- Avoid dexamethasone, unless fetus has CAH

- Adjust doses to keep maternal testosterone level at high normal for pregnancy

- Elective C/S reconstructive surgery has been done

- Pediatrician at delivery if baby diagnoses with CAH pre-natally