Case Based Urology Learning Program

Resident's Corner: *UROLOGY*

Case Number 3

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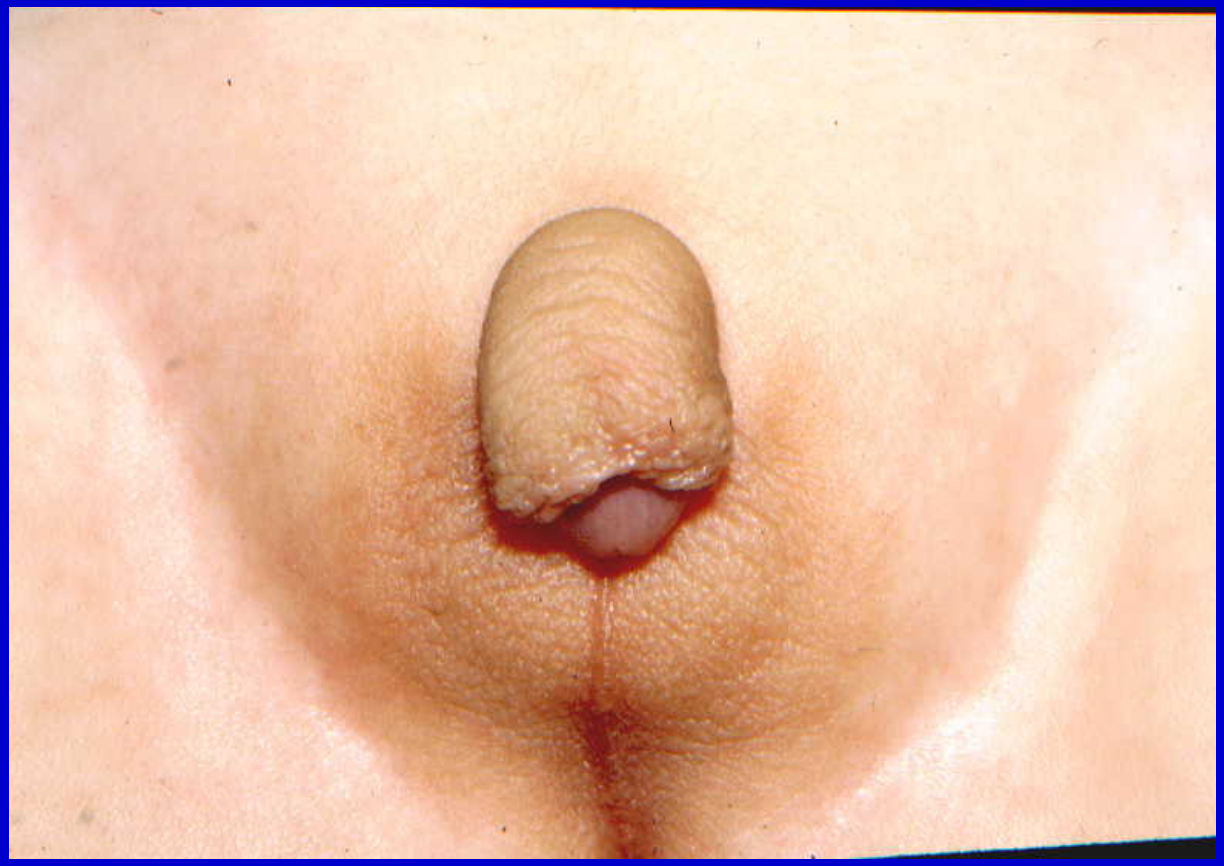
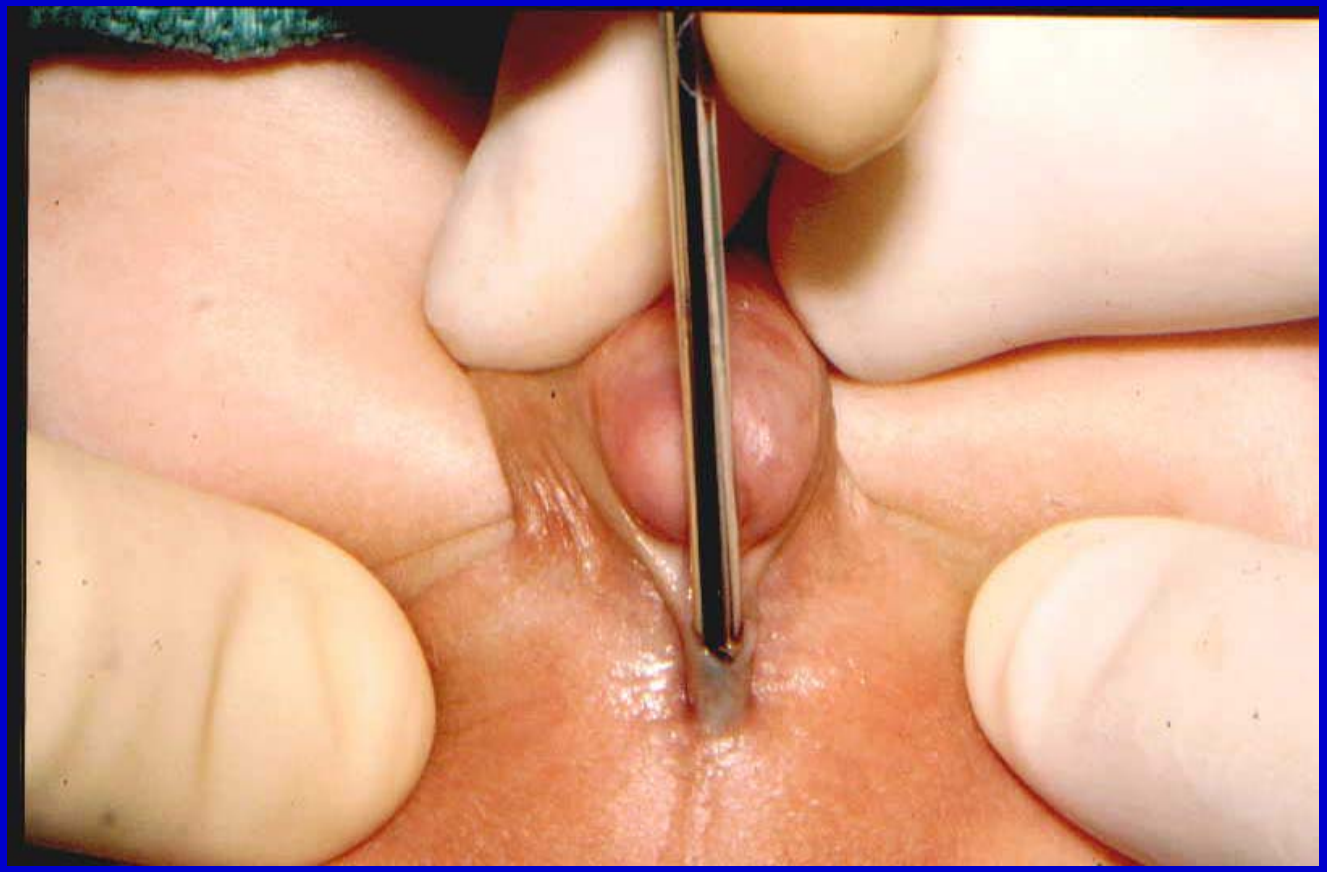
You are called to the nursery to see a newborn with hypospadias.
You do not feel testicles in the scrotum or in the inguinal canals.
Please review following images that illustrate the exam finding.





What is the most important medical consideration for this patient?

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The most important consideration is to rule out the possibility that this is a girl with congenital adrenal hyperplasia (CAH) because these patients can develop a life-threatening salt-wasting crisis in the first weeks of life if the diagnosis is missed.

Further history reveals that the mother underwent amniocentesis and the baby's karyotype is 46XX.

What is the differential diagnosis and what is the most likely diagnosis?

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With a 46XX karyotype the overwhelming likelihood is that the patient has 21 alpha-hydroxylase deficiency – a form of congenital adrenal hyperplasia (CAH) which accounts for 95% of CAH cases. Other possibilities include rarer forms of CAH, maternal exposure to exogenous androgens, placental aromatase deficiency, and ovotesticular DSD (aka true hermaphroditism).

DSD is now a commonly used term in the field of Pediatric Urology.

What does it stand for?

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DSD stands for Disorders of Sexual Development. This is the term which replaces “intersex” in the nomenclature recommended by the joint conference of the American and European pediatric endocrine societies. In this new system the disorders are classified as “46XX DSD” or “46XY DSD” based on the karyotype of the patient; or as “Sex-chromosome DSD” for those with anomalous karyotypes such as 45XO Turner syndrome.

A final category is “Ovotesticular DSD” for those with both ovarian and testicular tissue. This last category which used to be called “true hermaphroditism” is problematic for this nomenclature system because the most common karyotype in North America for this disorder is 46XX (in which case it is categorized as a “46XX DSD”) although it can also occur in patients with 46XY/46XX or 46XY karyotypes.

Because 21-alpha hydroxylase deficiency is the most likely diagnosis, what test should be ordered to confirm or exclude the diagnosis?

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Serum 17-hydroxyprogesterone. If this is elevated it confirms the diagnosis of CAH – the great majority of which are 21-alpha hydroxylase deficiency.

If 17-hydroxyprogesterone levels are normal and ovotesticular DSD is suspected, how would that diagnosis be confirmed?

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Levels of serum Mullerian inhibiting substance (MIS) should be measured. These are very sensitive and specific for the presence of testicular tissue. If they are elevated, then the patient likely has ovotesticular DSD and laparoscopic or open gonadal biopsies should be performed to confirm the diagnosis and remove the discordant gonadal tissue (depending on the gender assignment).

This patient is confirmed to have 21-alpha hydroxylase deficiency.

What is CAH generally and why do patients with 21-alpha hydroxylase deficiency develop ambiguous genitalia?

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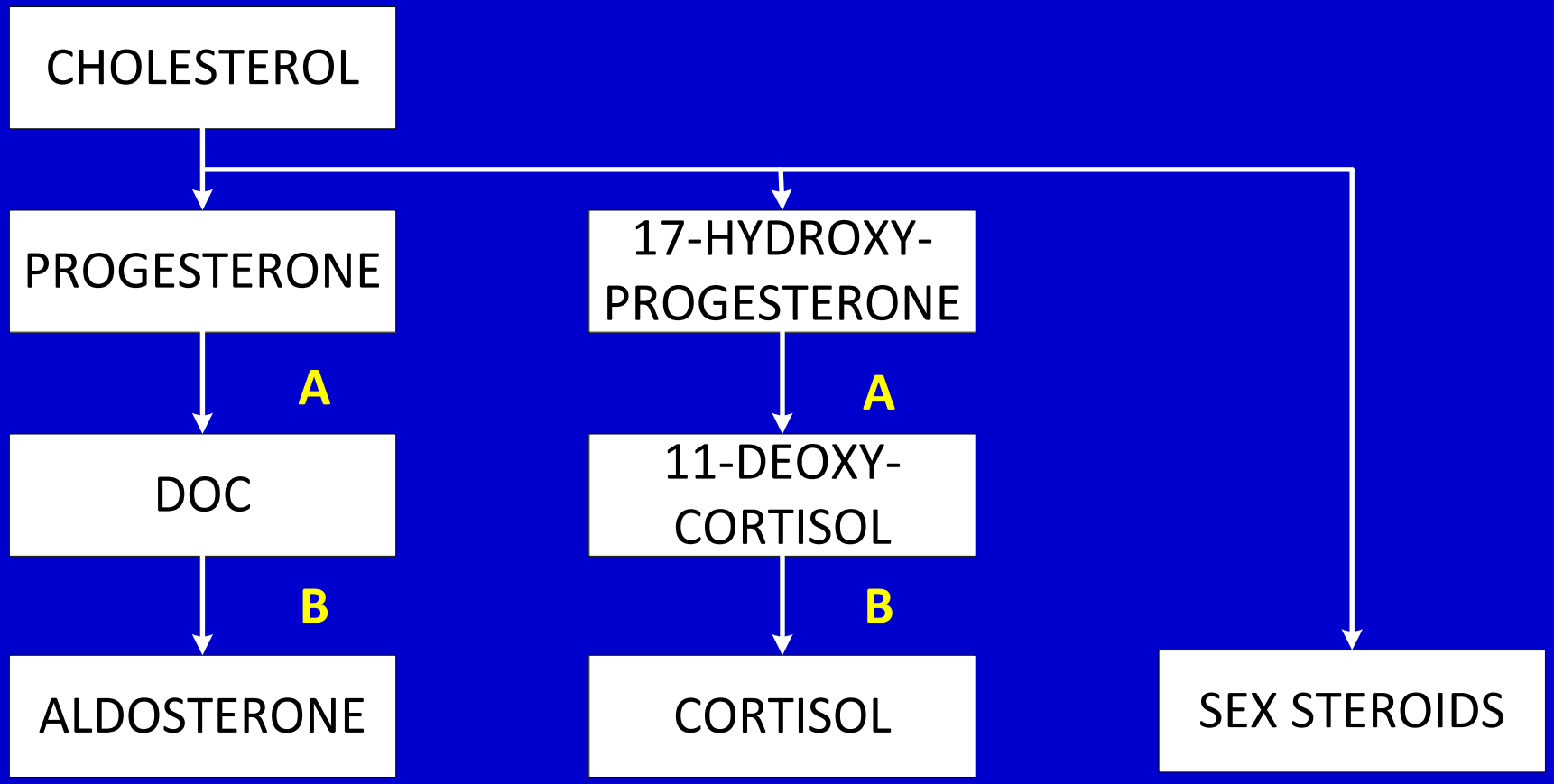
CAH refers to a group of disorders in which an enzymatic defect in the adrenal pathway from cholesterol to cortisol prevents normal cortisol synthesis. Since cortisol is under-produced, ACTH levels increase leading to adrenal hyperplasia. Serum levels of precursors to cortisol proximal to the enzymatic defect increase and, depending on the location of the defect in the biochemical pathways, may be converted to testosterone and/or aldosterone. As shown in the figure, those enzymatic defects (such as 21-alpha hydroxylase deficiency) that lead to increased shunting toward testosterone will cause ambiguous genitalia in girls.

A-21 ALPHA HYDROXYLASE **B-11 BETA HYDROXYLASE**



Why do some girls with 21-alpha hydroxylase deficiency develop salt-wasting?

Why do some girls with 21-alpha hydroxylase deficiency develop salt wasting?

21-alpha hydroxylase is needed for the production of aldosterone as well as cortisol so these patients may have decreased serum levels of mineralocorticoids. If the enzyme defect is mild, the adrenal hyperplasia and increased precursor levels may lead to sufficient mineralocorticoid production (simple virilizing CAH). But if the defect is severe enough that mineralocorticoid production is significantly impaired, then salt-wasting may occur (salt-wasting CAH). For the latter patients mineralocorticoid replacement may be required in addition to the corticosteroids that all CAH patients require.

What gender assignment is most often applied to these patients and why? What factors should be considered when gender assignments are made generally?

What gender assignment is most often applied to these patients and why? What factors should be considered when gender assignments are generally made?

The factors to consider in gender assignment are fertility potential, the challenges of genital reconstruction, and the likely ultimate gender identity of the patient. Virtually all 46XX individuals with CAH are assigned a female gender as they have normal ovaries and a uterus and can be fertile as females. However, the genital reconstruction can be quite difficult in highly virilized individuals. And while preliminary data suggests that gender dysphoria is rare for these women, sexual dysfunction is fairly common.

Selected Readings

Lambert SM, Vilain EJM, Kolon TF: A Practical Approach to Ambiguous Genitalia in the Newbord Period. *Urol Clin No Amer* 2010;37:195-205.

Topic:

Pediatric Urology

Subtopics:

Ambiguous Genitalia

Congenital Adrenal Hyperplasia