

LEARNING OBJECTIVES

- Review disorders of sexual development
- Understand the adrenal steroid biosynthesis pathway
- Learn a specific XY disorder of sexual development, 17 beta-hydroxysteroid dehydrogenase-3 deficiency

CASE SUMMARY

History: A 50-year-old Asian female presented with a mass in her left inguinal area enlarging rapidly over the past six months. She had noted masses in both inguinal areas for over ten years.

PMH: Primary amenorrhea and lack of breast development. Unmarried and no children. No significant family history, and her four sisters all had children. No parental consanguinity.

Physical Exam: Normal vital signs. Normal BP. Wt. 118 lbs, Height: 64 inches. No facial hair, axillary and pubic hair shaved, bilateral breast implants. Abdomen: 6 x 8 cm discrete, hard mass in the left upper inguinal area, mildly tender. Palpable, less than 2 x 2 cm non-tender mass deep in the right inguinal area. Genital: labia majora and minora along with clitoromegaly (1 cm in diameter at the base and 2 cm in length). Vaginal canal ended blindly, no cervix.

Labs*: (Hgb 11.4 g/dl), normal clinical chemistry, K normal, LDH 348 U/L (98-192), B-HCG 54.4 mIU/ml (< 0.5-2.67), AFP-serum 1.2 ng/ml (0-9.0). LH 32.5 mIU/ml (1.5-9.3), FSH 38.2 mIU/ml (1.6-8.0). Cortisol 0 min: 13.3, 60 min: 26.3. TSH 0.86. *reference ranges are for males.

Karyotype 46, XY.

Pathology/Cytology: Left mass was a testis replaced by tumor consistent with a seminoma, stage T1NXMX. There was extensive necrosis, mildly pleomorphic cells, clear cytoplasm with nuclear enlargement, + CD117 stain. The right mass was a testis with severe tubular atrophy, absence of spermatogenesis (loss of all germ cells), and nodular hyperplasia of Leydig cells.

Clinical Course: The patient underwent bilateral orchiectomy. Offered observation versus radiation therapy for the seminoma. Final genetic analysis and counseling is pending.

REFERENCES

1. Conte, F. & Grumbach, M. *Greenspan's Basic & Clinical Endocrinology, Ed 8th.* (2007)
2. Hughes, I et al. *Clinical Endocrinology.* 2007. 67, 20-28.
3. Rosler, A.. *Pediatr.Endocrinol.Rev.* 3 Suppl 2006. 3:455-61.
4. Faienza, M.F., Giordani, L., Delvecchio, M., & Cavallo, L. *J.Endocrinol.Invest.* 2008. 31, 85-91.
5. Lindqvist, A.. Hughes, I.A. & Andersson, S. *J.Clin.Endocrinol.Metab.* 2001. 86, 921-923.
6. Mains, L et al. *Fertility and Sterility.* 2008. 89 (1) 228.13-18.

IMAGES and Steroid Hormones



Figure 1. CT chest/abdomen/pelvis: bilateral complex inguinal masses, both predominately solid and neither containing bowel. Absent uterus. No evidence of pulmonary nodules.



Figure 2. A. Tumor mass replacing entire left testicle (270g). B. Right Testicle with advanced tubular atrophy.

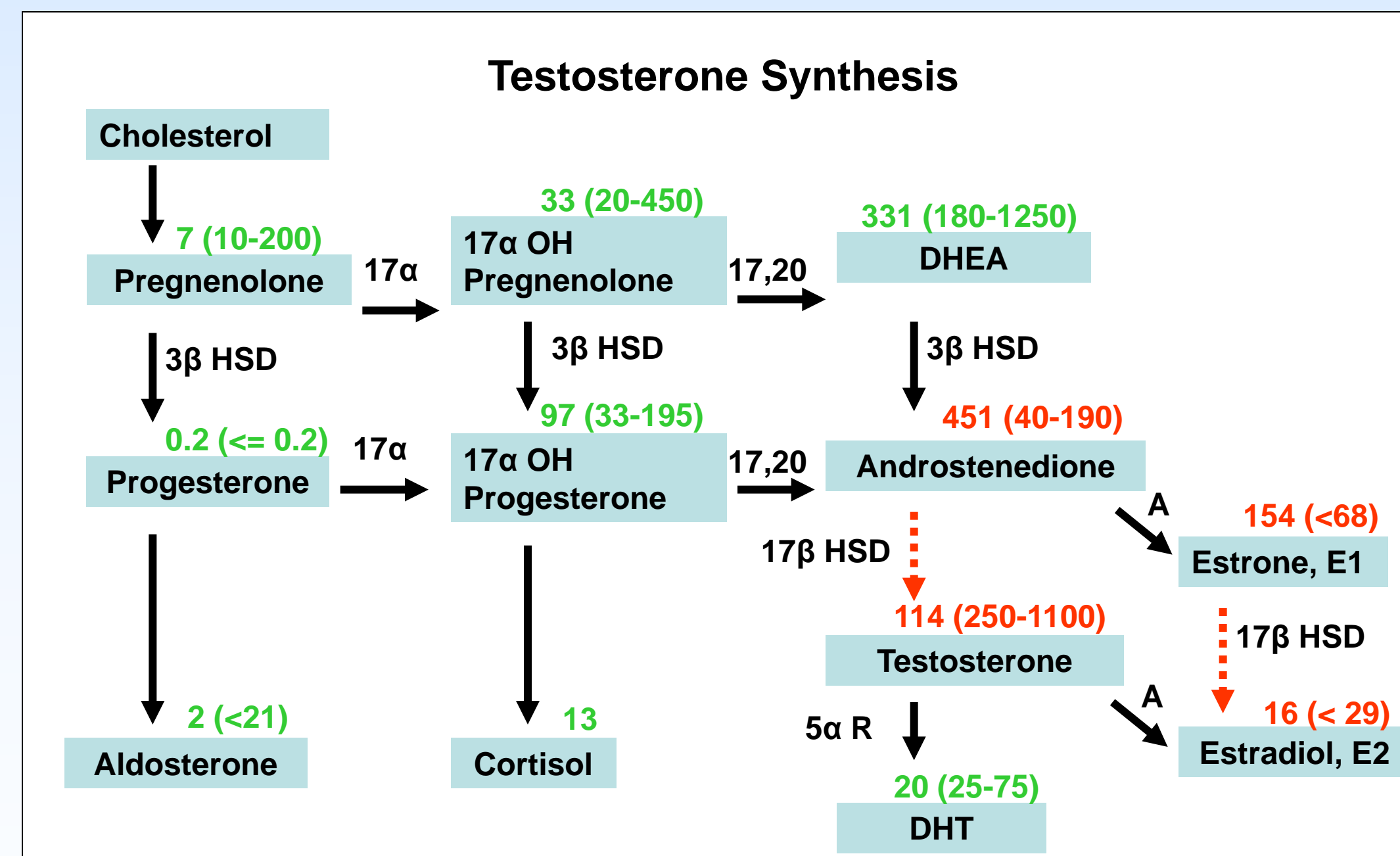


Figure 3. Testosterone (T) is synthesized from cholesterol via five enzymatic steps. Final step Androstenedione (A) to T takes place in the Leydig cells of the testes by enzyme 17β-HSD-3: 17 beta-hydroxysteroid dehydrogenase-3 (formerly 17β reductase). 3β HSD: 3 -hydroxysteroid dehydrogenase. 17α: 17α -Hydroxylase. 17,20 Lyase. 5α R: 5-alpha reductase. A: Aromatase. DHEA: dehydro-epiandrosterone. Numbers= patient's results. All values in ng/dL except E1, E2 (both pg/dL), and cortisol (mcg/dL). Modified from UpToDate 2009 "Synthetic pathways for adrenal steroid synthesis."

DISCUSSION

Male pseudohermaphroditism/Male Disorders of Sexual Development*

XY genotype, presence of both testes, incomplete development of genital ducts or external genitalia.

A. Testicular unresponsiveness

- Leydig cell agenesis or hypoplasia
- LH receptor defect
- Atrophic testis

B. Mullerian Inhibiting Factor Defects

C. Dysgenetic testes (i.e. SRY gene mutation, testicular regression syndrome, WAGR)

D. Endocrine Disruptors

E. Defects in androgen-dependent target tissues

F. Errors in testosterone biosynthesis

- 5-alpha reductase deficiency
- **17 beta-hydroxysteroid dehydrogenase-3 defect**
- Other adrenal enzyme defects

*Modified from Conte FA, Grumbach MM: Table 15-3.

17 Beta-hydroxysteroid dehydrogenase-3 deficiency

Clinical characteristics:

- born with ambiguous or female external genitalia
- primary amenorrhea
- inguinal masses
- Degree of virilization during puberty (peripheral conversion of A to T by a related enzyme, 17-hydroxysteroid dehydrogenase-5)

Biochemical findings:

- High levels of Androstenedione (A), low levels of T, Low T:A ratio (<0.4 in one case series of effected patients)
- Elevated E1, Low E2, Low E2 to E1 ratio
- Need HCG stimulation test to show enzyme defects before puberty

Differential diagnosis:

- 5-alpha reductase deficiency, T:DHT ratio is high (>20: 1)
- Androgen Receptor Defects: High T and LH. No virilization at puberty in complete androgen insensitivity syndrome

Genetics:

- Gene for 17β-HSD-3 is on chromosome 9q22
- 20 mutations have been reported, rare, no incidence data
- Autosomal recessive inheritance
- Females are asymptomatic

Treatment:

- Infants assigned a male gender, treat with testosterone
- If female gender assigned, treat with estrogens; corrective surgeries such as clitoroplasty or vaginal dilation
- Removal of the cryptorchid testes to avoid neoplastic transformation