Transgender Care

Clinical Case Applicability: reproductive endocrinology, hormone therapy, transgender care

Learning Objectives:
1. Understand the principles of sex hormone synthesis and regulation
2. Understand the mechanisms and pathways of hormone therapy

Clinical Presentation: transgender individuals often report gender incongruence throughout their lifetime that can occur before or after puberty.

How are sex steroids synthesized and regulated?
Regulation: the synthesis and secretion of estrogens and androgens are regulated by the HPO axis: hypothalamus → GnRH → anterior pituitary → FSH/LH → ovary

Synthesis: sex hormones are derived primarily from cholesterol and regulated by LH secretion (figures 1 & 2)
- cholesterol → pregnenolone → 17OH-pregnenolone → DHEA → **androstenedione**
  - in females, this process occurs 50:50 in the adrenal gland and ovarian theca cells
  - in males, this process occurs primarily in the Leydig cells of the testis
- androstenedione is then converted to estradiol or testosterone
  - in females, regulated by FSH and occurs in ovarian granulosa cells: androstenedione → *aromatase* → estrone → *17β-hydroxysteroid dehydrogenase* → estradiol
  - in males, androstenedione → *17β-hydroxysteroid dehydrogenase* → testosterone
    In the periphery: Testosterone → *5α-reductase*→ dihydrotestosterone (DHT)
    → *aromatase* → estradiol

What are the roles of estradiol and testosterone?
Estradiol is the major female sex hormone and responsible for:
- maintenance and development of primary female reproductive organs
- development of female secondary sexual characteristics
- regulating the female reproductive cycle

Testosterone is the primary male sex hormone. In males, it is responsible for:
- development of male primary reproductive tissue
- development of secondary male sexual characteristics

What is the role of hormone therapy?
Male-to-female hormone therapy: primary goal is to both decrease testosterone and increase estrogen to female physiological range
- estradiol: acts on nuclear estrogen receptors to mediate gene transcription and promote:
  - ↓body hair, ↓spontaneous erections, ↓muscle mass, redistribution of body fact, breast development
  - Important to maintain below supra-physiological levels (<200pg/mL) secondary to thromboembolic risk & liver dysfunction
- antiandrogens: inhibits secretion and activity of testosterone which allows for ↓doses of estradiol therapy
  - Spironolactone most common – blocks androgen receptors & decreases androgen synthesis
  - Occasionally 5α reductase inhibitors (finasteride, dutasteride) are used

Female-to-male hormone therapy: goal is to increase testosterone to male physiological range
- testosterone: acts on nuclear androgen receptors to mediate gene transcription and promote:
  - cessation of menses, ↑facial/body hair, ↑muscle mass, clitoromegaly, redistribution of fat, deepening of voice

What is the role of gender-affirming surgery?
- some patients may elect gender-affirming surgery which includes chest reconstruction surgery and reproductive/genital surgery
- surgeries are generally performed after long-term maintenance on hormone therapy by interdisciplinary teams involving gynecological surgeons, urologists and plastic surgeons as well as reproductive endocrinologists, primary care physicians, psychiatrists and psychologists

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Figure 1

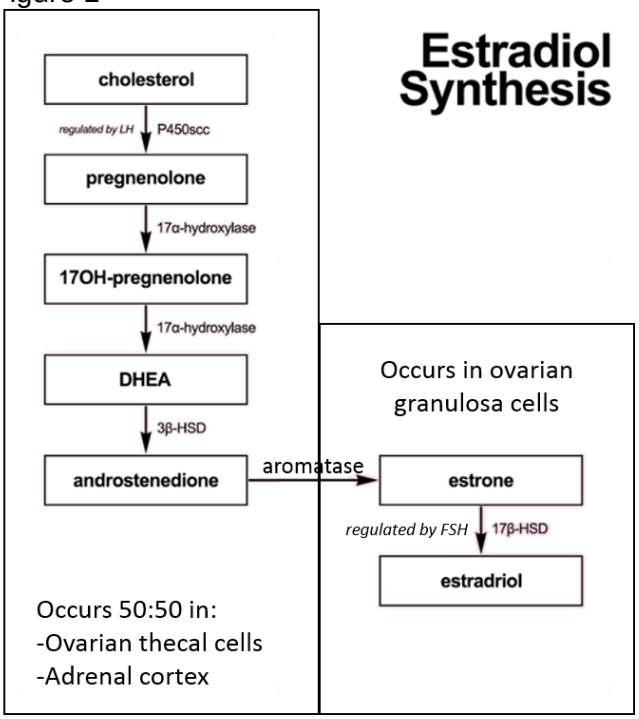
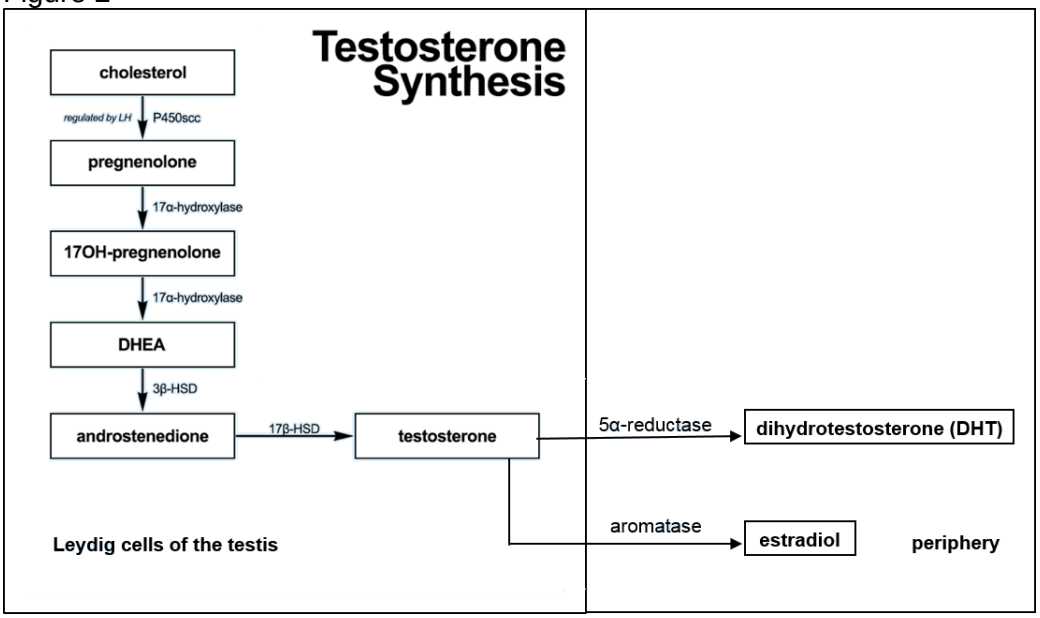


Figure 2



References:

- Hoffman, BL, Schorge, JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Chapter 15 Reproductive Endocrinology. *Williams Gynecology, 3e* New York, NY: McGraw-Hill; 2016.
- Hembree WC et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guidelines. *J Clin Endocrinol Metab* 2017, 102(11):3869-3903.
- Matsumoto AM, Anawalt BD. Male reproductive physiology. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (2018)
- Crissman HP, Berger MB, Graham LF, Dalton VK. Transgender Demographics: A Household Probability Sample of US Adults, 2014. Am J Public Health. 2017 Feb;107(2):213-215.
- Strauss JF and Barbieri RL. Yen & Jaffe's Reproductive Endocrinology, 8th edition. 2019. Elsevier, Philadelphia, PA.
- Grabber, E. Hormonal therapy for women with acne vulgaris In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (2018)