

Lecture Supplement #31, Hirsutism and Virilization

- **Hair Growth Physiology**
 - Human hair is of three varieties
 - Lanugo (fine, soft fetal hair)
 - Vellus hair (soft, relatively unpigmented hair)
 - Terminal hair, i.e., large, coarse, pigmented, which forms from vellus hair under androgen influence
 - At puberty, a surge in androgen secretion causes the vellus on some parts of the body to convert to terminal hair.
 - Terminal hair follicles are further classified by their relative sensitivity to androgen
 - Asexual (scalp, eyebrows, eyelashes) which is sex steroid independent
 - Ambisexual (pubic hair, axillae) which is responsive to lower levels of androgen
 - Sexual (chest, face, upper pubic triangle, nose, ears, etc.) from less sensitive follicles that need higher levels of sex steroid
 - However, once terminal hairs appear, only a small amount of androgen is required to maintain them
 - Hair follicle activity (**see handout**)
 - Grows in cycles of alternating activity and inactivity, therefore, treatment times, as with spironolactone (Aldactone), must be lengthy (see below)
 - Three phases
 - Anagen (growth phase)
 - Catagen (involution)
 - Telogen (resting phase)
 - The effect of androgen is to increase:
 - hair shaft diameter
 - the number of follicles in anagen
 - the transition of vellus hair to terminal hair
 - The actual number of follicles/unit of skin is genetically determined at birth
 - Follicles regenerate from dermal papillae, therefore the dermal papillae must be destroyed to cure hirsutism, (which is why plucking hairs doesn't cure hirsutism)
- **Androgen Metabolism**
 - Androgens play three essential roles in female reproductive function:
 - Precursors of estrogen synthesis
 - Stimulation and maintenance of ambisexual hair growth
 - Drive female libido
 - Three sources of androgen in the female are: (**see handout**)
 - Ovary (controlled by pituitary LH)
 - Adrenal (controlled by pituitary ACTH)
 - Peripheral conversion of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstendione (A'D).
 - The principal androgens
 - Dihydrotestosterone (DHT)
 - Most potent (2xT)

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- Derived primarily from peripheral conversion of A'D which requires the enzyme, 5-alpha reductase
- 5-alpha reductase activity can be indirectly measured by assay of 3 alpha DIOL-G
- Testosterone (T)
 - Second most potent androgen
 - Only 1% of T in female is free, compared to 3% in male
 - T is the marker for androgen of ovarian origin, because:
 - 25% of T comes directly from the ovary
 - 50% of T comes from peripheral conversion of A'D, 50% of which comes from the ovary
- Androstendione (A'D)
 - Only 20% of androgen activity of T, but has potential for conversion to T
 - Equal amounts produced by ovary and adrenal
 - Diurnal variation up to 50% 2^o to variations in ACTH
- Dehydroepiandrosterone, dehydroepiandrosterone sulfate (DHEA/DHEA-S)
 - Weak (3% the activity of T)
 - Androgenic activity results from peripheral conversion to more potent substances
 - Both DHEA and DHEA-S are secreted directly and almost exclusively by the adrenal
 - DHEA-S is the marker for androgen of adrenal origin since DHEA shows greater circadian rhythm.
- **Clinical Signs of Excess Androgen**
 - Although highly variable, in general, as androgen levels rise, there is a progression of symptoms from:
 - cosmetically disturbing hirsutism/acne to,
 - mild disturbances of menstrual function to,
 - infertility, amenorrhea, dysfunctional uterine bleeding, to,
 - virilization
 - Hirsutism = the presence of terminal hair in locations where it is normally not found in the female, particularly in the mid-line.
 - More common than virilization
 - Usually associated with milder androgen excess, a gradual onset, and usually not associated with either a severe enzymatic defect or neoplasm.
 - Mildest form = upper lip and chin
 - Increasing severity involves cheeks, chest, abdomen, inner thighs, lower back, intra-gluteal areas
 - Hypertrichosis differs from hirsutism in that it represents generalized increased body hair not restricted to a sexual distribution, and is predominantly vellus
 - Virilization = in addition to hirsutism, temporal balding, voice changes, clitoral enlargement, acne, increased muscle mass, decreased breast size, amenorrhea
 - Relatively uncommon

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- Associated with T levels above 2ng/mL
- Occurs over relatively short time
- When present, one must always suspect androgen secreting neoplasm.
- **Clinical Causes of Hirsutism/Virilization(see handout)**
 - Idiopathic hirsutism
 - Excess male pattern hair growth in females who have normal ovulatory menses and normal androgen levels
 - Results from elevated 5-alpha reductase levels in skin
 - Careful evaluation for ovulatory dysfunction often reveals only a few that can truly be classified as idiopathic.
 - **Polycystic Ovarian Syndrome (PCOS)/Functional Ovarian Hyperandrogenism (FOH)**
 - The most common of the anovulatory conditions, the most common of all endocrine disorders, (6% of reproductive age females), and the most common cause of female infertility in the United States.
 - **PCOS is the most common cause of androgen excess seen in primary care, and, therefore, the most common cause of hirsutism in reproductive age women.**
 - The modern concept of this condition is a female with hyperandrogenism and chronic anovulation, without other etiology for the oligo-ovulation and hyperandrogenism such as an androgen secreting tumor, or non-classical adrenal hyperplasia.
 - May or may not have: ovarian enlargement, oligomenorrhea, hirsutism, obesity and an altered LH:FSH ratio
 - Approximately 30% have cyclic bleeding although almost all are anovulatory resulting in chronic unopposed estrogen stimulation to the endometrium.
 - Most women with PCOS/FOH have gonadotropic dependent increased ovarian androgen production as a result of an enzymatic dysregulation of the ovary.
 - The dysregulation is thought to be a result of hyperinsulinemia, insulin resistance being a key component of PCOS/FOH.
 - Insulin resistance, a reduction in the tissue response to insulin, affects up to ½ of all women with PCOS and leads to compensatory hyperinsulinemia.
 - Insulin augments the the stimulating effect of LH on the growth and androgen secretion of ovarian theca cells and inhibits the production of SHBG.
 - For this reason, women with PCOS and insulin resistance are at increased risk for beta cell dysfunction and subsequent impaired glucose tolerance or diabetes.
 - Variations
 - Stein-Leventhal Syndrome = bilateral ovarian enlargement, normal adrenal function, oligo/amenorrhea, infertility, obesity, and hirsutism without virilization
 - Hyperthecosis = (see below)
 - HAIR-AN Syndrome = HyperAndrogenism, Inulin Resistance, Acanthosis Nigricans, and T levels 100x normal

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- With elevated DHEA-S
- Pathophysiology
 - At puberty, with rising LH levels, the combination of severe insulin resistance, and LH stimulation, results in ovarian hyperandrogenism from hyperplastic thecal and stromal cells of the ovary
 - Essential anatomical feature is arrested follicular maturation, predominance of thecal cells, deficiency of granulosa cells, and stromal hyperplasia
 - The central abnormal hormonal feature is deficient estrogen production and excess androgen secretion by the ovary
 - The androgen (androstenedione) is peripherally converted to estrone which maintains high LH levels by (+) feedback, and low FSH levels by (-) feedback, thus altering the LH:FSH ratio
 - The FSH is sufficient to start follicle growth, but not enough to increase the number of LH receptors.
 - The multiple follicles, therefore, do not respond to the elevated LH, extending their life, and producing the anatomical changes described above, while the stroma responds to the elevated LH by producing androstenedione
 - The gross appearance of the ovary is typically enlarged, tense, oval, with a thick, tough, white tunica (oyster like), with multiple follicle cysts in the stroma
- Diagnosis
 - At present, PCOS is a diagnosis of exclusion, requiring clinical or biochemical evidence of hyperandrogenism and ovulatory dysfunction and the absence of other causes.
 - Ultrasound visualization of “polycystic” ovaries is NOT required, because women who have polycystic ovaries are not necessarily anovulatory, and the ovaries of women who meet the criteria of PCOS may not appear to be polycystic.
 - Because of the unlikely but real possibility of a neoplastic etiology, focus first on palpable adnexal masses and signs of Cushing syndrome.
 - If neither is present, order serum total testosterone, serum DHEAS, 17-hydroxyprogesterone, prolactin, and TSH if history or exam suggest this diagnosis.
 - If these are normal (90% of cases), life threatening and other serious conditions have been R/O.
 - All women with PCOS should be screened for glucose intolerance with a 2 hr. glucose level after a 75-g fasting glucose challenge, and for dyslipidemia with a profile including total cholesterol, LDL, HDL, and triglyceride determination.
- Management (**see treatment algorithm attached**)
 - Treating insulin resistance
 - Metformin is an insulin sensitizing agent that reduces glucose production by the liver

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- Metformin use in PCOS will in most, but not all cases, lower circulating insulin levels, reduce weight, improve insulin resistance, or induce ovulation.
- Facilitating ovulation
 - Even women who do not desire fertility stand to gain by ending anovulation which decreases their risk of endometrial cancer
 - Clomiphene citrate has been used for decades to induce ovulation in women with PCOS (**see Lecture Supplement #32**)
 - Pretreatment with metformin may enhance ovulation induction with clomiphene.
- Addressing hirsutism
 - Best approached by a combination of medical and mechanical means
 - After treating anovulation and androgen production, androgenic effects at the level of the pilosebaceous may be antagonized by such agents as androgen receptor antagonists (flutamide, spironolactone) or 5α reductase inhibitors (finasteride)
 - Once medical therapy has been maintained for 6 to 12 months, electrolysis and lasers may be used to permanently remove hair.
 - If pregnancy is not desired, use OC's (particularly drospirenone and ethinyl estradiol [Yasmin]) to reduce LH, which will reduce A'D and T clearing acne, preventing new hair growth, endometrial hyperplasia, and promoting cyclic bleeding
 - Weight loss to interrupt PCOS cycle at the adipocyte and raise level of SHBG also reduces insulin resistance.
- Hyperthecosis
 - A histologic diagnosis in which islands of luteinized thecal cells exist within the ovarian stroma
 - Similar to PCOS, but usually with higher androgen levels
 - LH:FSH 1.0 (vs. 3.0 for PCOS)
 - Most are anovulatory, and unresponsive to clomiphene (Clomid/Serophane)
 - Unlike PCOS may persist past menopause
 - Insulin resistance is more pronounced than with PCOS
 - Diagnosis usually by history, degree of virilization, and pathology report after oophorectomy or wedge resection
- Androgen secreting (Sertoli-Leydig cell) tumors
 - Rare, but the most common virilizing neoplasm of the ovary
 - 75% are in the reproductive years (15-45), but 95% are unilateral, which allows preservation of reproductive function.
 - Ovarian neoplasms have the potential to produce estrogens or androgens, since the stroma and cortex have a common origin.
 - 75% produce androgen and cause rapid loss of secondary sexual characteristics and signs of virilization
 - Surgical removal results in regression of male characteristics (except for voice changes), frequent return of menses, and even occasional (10%) pregnancy rate

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- Adrenal enzyme deficiencies
 - Congenital adrenal hyperplasia of adult onset is 2^o to deficiencies of 21-hydroxylase or 11-beta hydroxylase
 - Excess ACTH 2^o to deficient cortisol negative feedback results in overproduction of C19 (androgenic) steroids
 - Clinical picture similar to PCOS
 - Diagnosis is by ACTH Stimulation Test which utilizes the measurement of 17-hydroxy progesterone after administration of ACTH
- Adrenal androgen excess (Cushing's syndrome/disease)
- Adrenal adenoma/carcinoma (rare in females)
- Miscellaneous causes of hirsutism
 - Drugs
 - Phenytoin (Dilantin)
 - Diazoxide (Hyperstat)
 - Minoxidil (Rogaine)
 - Danocrine (Danazol)
 - Alterations in sex hormone binding globulin
 - Obesity
 - Hypothyroidism
- **Therapy for the Patient with Androgen Excess**
 - Principles
 - Increase SHBG to decrease bioactive androgens
 - Decrease serum androgen
 - Block end-organ response
 - Cosmesis
 - Surgical removal of ovarian and adrenal neoplasms with preservation of reproductive function where possible.
 - Medical treatment for endocrinopathies
 - Weight loss for obesity
 - PCOS/FOH (see above)