Hirsutism and Hyperandrogenemia

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Objectives

- Physiology of androgen production in women
- Discuss clinical manifestations of hyperandrogenemia
- Define degree of hirsutism (Ferriman-Gallwey)
- Discuss the most common cause of hyperandrogenemia in adolescence-Polycystic ovarian syndrome
- Discuss management and treatment of hyperandrogenemia

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Sources of androgen production in women

- In females, androgens originate from three primary sources:
  - (1) the ovarian theca,
  - (2) the adrenal cortex (zona reticularis),
  - (3) within end organs by peripheral conversion.
- The major androgens include dehydroepiandrosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone, and dihydrotestosterone, with the latter two having the highest affinity for the androgen receptor and the greatest potency
  - In healthy women, testosterone is largely bound by sex hormone binding globulin and albumin, leaving only approximately 1% freely circulating as bioactive “free testosterone
  - 5alpha-reductase converts testosterone to the highly potent dihydrotestosterone.

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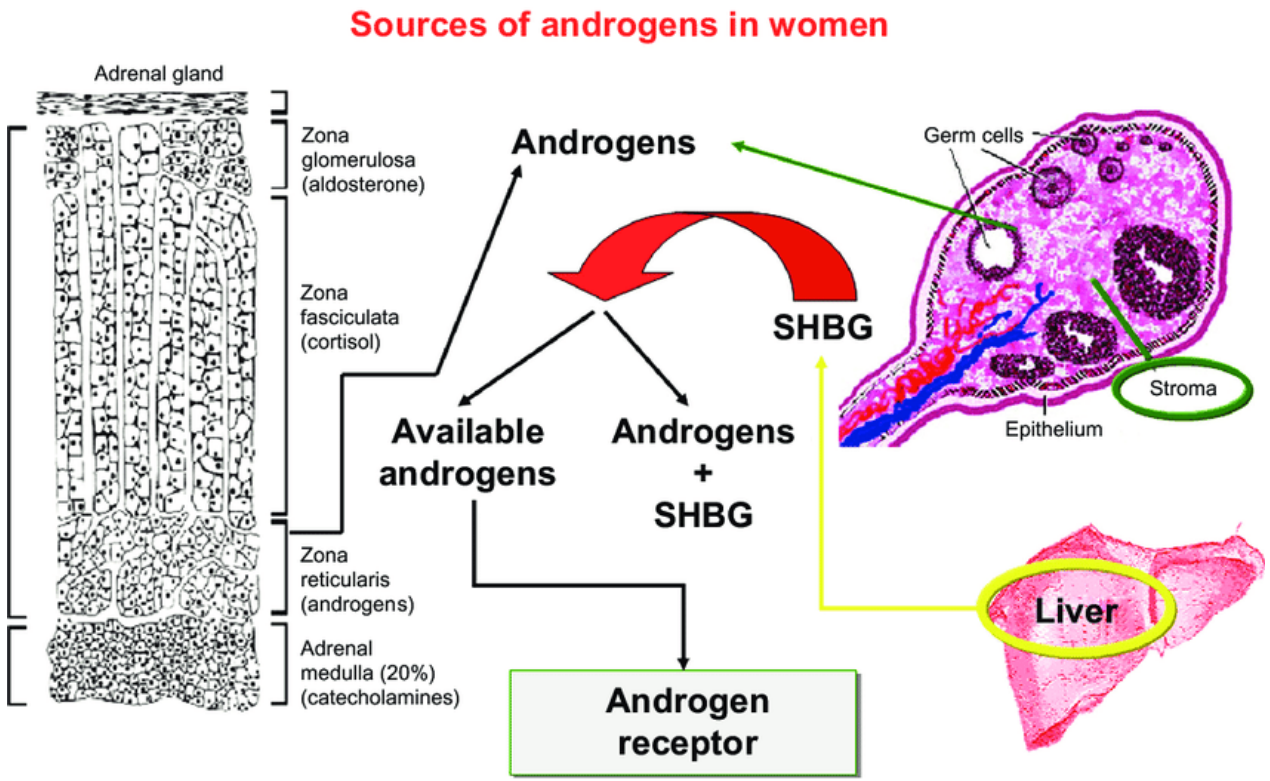
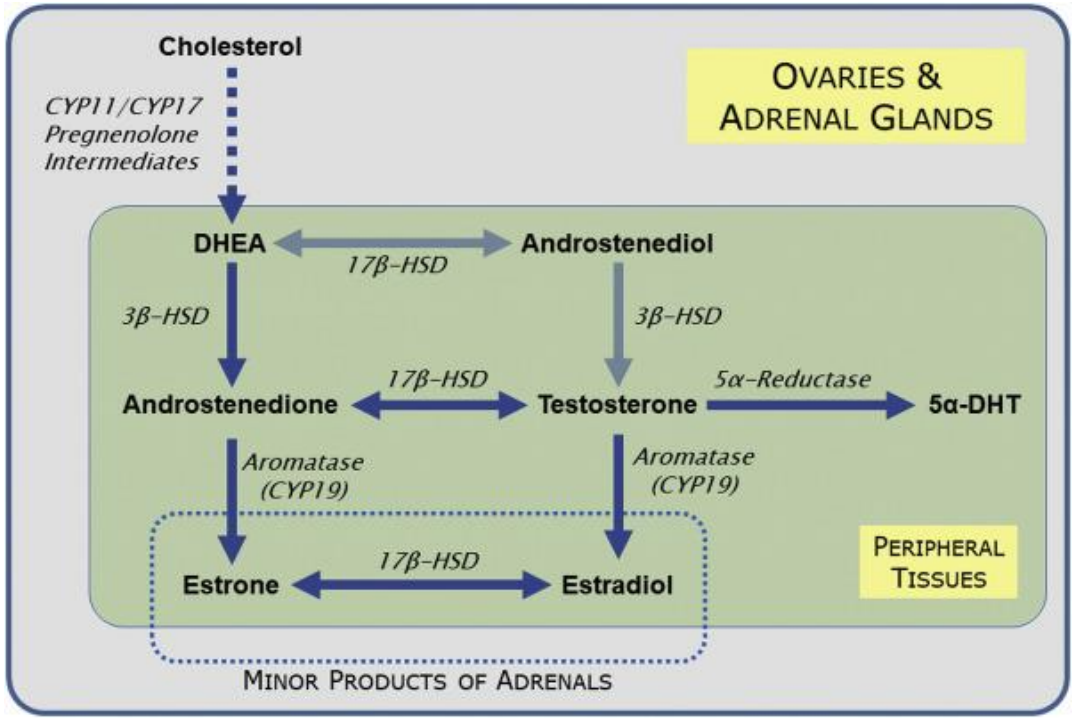
Sources of androgens in women





Only testosterone and DHT bind to the AR. DHEA, DHEAS and androstenedione are inactive precursors capable of conversion to more potent androgens and estrogens in peripheral tissues.

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Androgens during Development

- During childhood, DHEA and DHEA-S concentrations remain low.
- Between 6-8 years of age, these levels begin to increase and characteristics of adrenarche begin to develop.
- Peak DHEA-S concentrations occur between 20-30 years of age and then begin to decline.
- Adrenarche occurs independently from puberty

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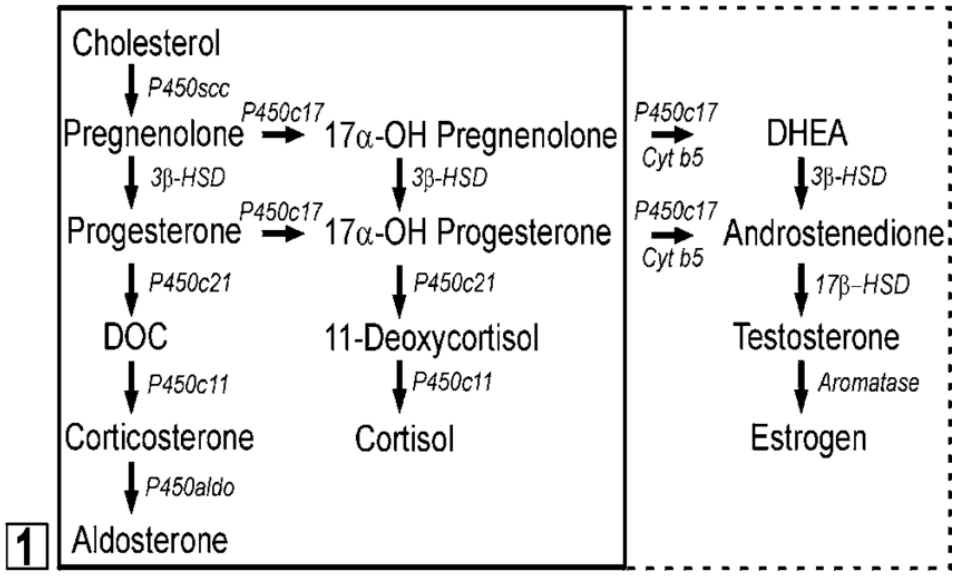
Regulation of Steroidogenesis

- Controlled by hypothalamic-pituitary-target organ axis
- LH stimulates ovarian theca cells to produce androstenedione, which then diffuses into granulosa cells
  - FSH induces expression of aromatase which converts androstenedione to estrogen
- ACTH provides trophic stimulation to the adrenal cortex



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Adrenarche

- 3B activity decreases while cytochrome b5, cytochrome P450, and DHEA-S increases to favor conversion of 17OHPregnenolone to DHEA and DHEA-S
- Pubic/axillary hair, body odor, and acne

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Hyperandrogenemia

- Hirsutism and acne are the most common symptoms
- Hirsutism affects 5–10% of reproductive-aged females
- Acne vulgaris is a multifactorial skin condition of varying severity that affects as many as 90% of all adolescents
- In patients with symptoms of androgen excess, PCOS is the most common cause

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Causes of hyperandrogenemia in Prepubertal and Postpubertal females

- Adrenal
  - CAH
  - Cushing's Syndrome
  - Adrenal Tumor
  - Inherited glucocorticoid resistance
  - Bilateral Adrenal Dysfunction
- Ovarian
  - PCOS
  - Ovarian tumor
  - Gonadal enzyme deficiency
  - Aromatase deficiency
  - Aberrant Gonadal differentiation

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Evaluation of Hyperandrogenemia

Medical History

- age of thelarche, adrenarche, and menarche
- off-label use of anabolic steroids or testosterone
- menstrual history, including frequency and duration.
- History of premature adrenarche and low birth weight.
- A history of rapid onset of virilization is more concerning for androgen secreting tumors.
- Obese?
- A family history of hirsutism, severe acne, PCOS, or obesity also should be recorded..

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Physical Exam

- Body mass index, blood pressure, and signs of hyperandrogenism
- assess for signs of insulin resistance, such as hypertension, obesity, centripetal fat distribution, skin tags, and acanthosis nigricans.
- Examination of androgen-sensitive skin areas such as the face, chest, abdomen, and back provide an assessment of the degree of hirsutism and can be used to chart patient progress over time
- Modified Ferriman–Gallwey scoring evaluates nine areas of the body; a score greater than 8 is indicative of hirsutism.
- Grading systems for acne include quantity (mild, moderate, or severe), location, and quality
- Clitoromegaly

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Hirsutism

- Defined as excessive terminal hair growth in a distribution typically seen in adult men (face, sternum, lower abdomen, back, and thighs)
- Growth of sexual hair is dependent on the action of androgens on hair follicles and sebaceous glands
- Testosterone and DHT act through AR in the dermal papilla to increase hair follicle size

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Modified Ferriman-Gallwey Scoring System

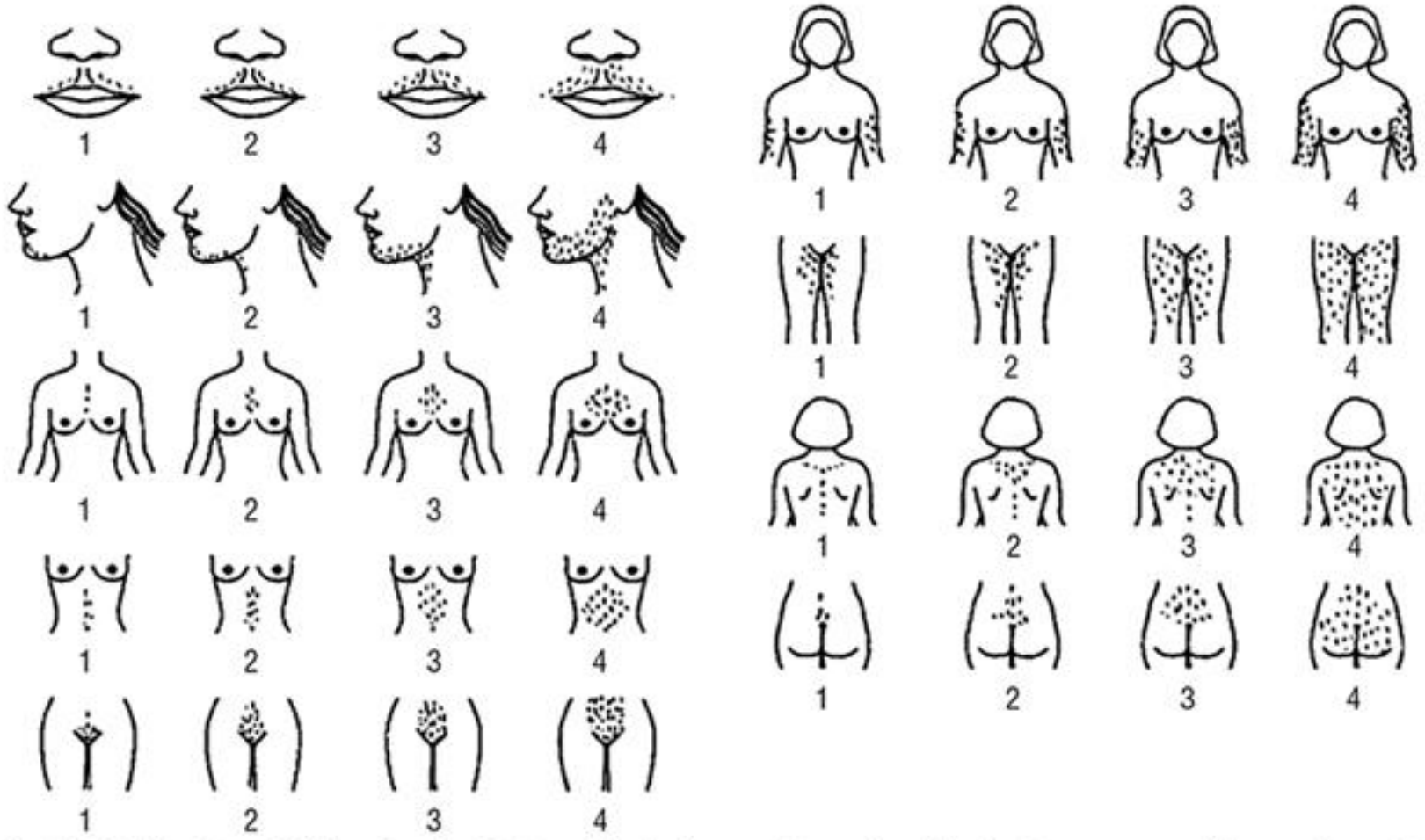

Figure 2. Modified Ferriman–Gallwey Scoring System. Nine body areas (upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back and thighs) are scored from 1 (minimal terminal hairs present) to 4 (equivalent to a hairy man). If no terminal hairs are observed in the body area being examined the score is 0 (left blank). Clinically terminal hairs can be distinguished from vellus hairs primarily by their length (eg, greater than 0.5 cm) and the fact that they are usually pigmented. (Reprinted from Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Hum Reprod Update 2010;16:51–64.)

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Evaluations

- Measurement of total testosterone and free testosterone, and screening for nonclassic congenital adrenal hyperplasia with a 17-hydroxyprogesterone test
  - Early morning sample for 17OHP
  - a level greater than 200 ng/dL is suggestive of nonclassic congenital adrenal hyperplasia
- Total testosterone can be affected by diurnal rhythms, phase of menstrual cycle, and sex hormone binding globulin concentrations
  - Should be obtained days 3-5 of menstrual cycle
  - SHBG levels are suppressed by hyperinsulinemia and androgen excess itself.
- Total testosterone levels greater than 200 ng/dL are suggestive of a virilizing tumor and should prompt pelvic ultrasonography.

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Evaluations

- ACTH stimulation test for confirmation of nonclassic congenital adrenal hyperplasia and DHEAS to rule out adrenal neoplasm
  - Laboratory use of high-quality radioimmunoassays are recommended rather than enzyme-linked immunosorbent or chemiluminescent assays, which have poorer sensitivity

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Evaluations

- Pelvic ultrasonography is not routinely indicated unless serum androgen levels or the degree of virilization is concerning for an ovarian tumor
  - The finding of polycystic ovarian morphology on ultrasonography has a prevalence in adolescent girls of 30–40% and alone is not predictive of the presence or future development of PCOS
- Adrenal CT if concerned for adrenal tumor

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Differential Diagnosis of Hirsutism

- PCOS
- Nonclassical CAH (1.5-2.5%)
- Androgen secreting tumors (0.2%)
- Cushing's
- Hyperprolactinemia
- Acromegaly
- Thyroid dysfunction
- Idiopathic (8% of women)-due to abnormal peripheral metabolism of androgens (increased 5alpha reductase in the skin or altered AR activity)

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Causes of Hyperandrogenemia

Polycystic Ovarian Syndrome (PCOS)

- most common cause of persistent hyperandrogenism beyond early puberty in adolescent girls and women and is estimated to affect 6–15% of reproductive-aged women
- Pathophysiology:
  - chronically elevated luteinizing hormone and insulin levels lead to increased androgen production within the ovarian theca.
  - hyperinsulinemia suppresses hepatic production of sex hormone binding globulin, which results in increased levels of free testosterone
  - There is a great deal of overlap between the symptoms of PCOS and those of normal puberty (eg, irregular menses, acne, polycystic ovarian morphology on ultrasonography), which makes the diagnosis of PCOS in the adolescent difficult.

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PCOS Pathophysiology

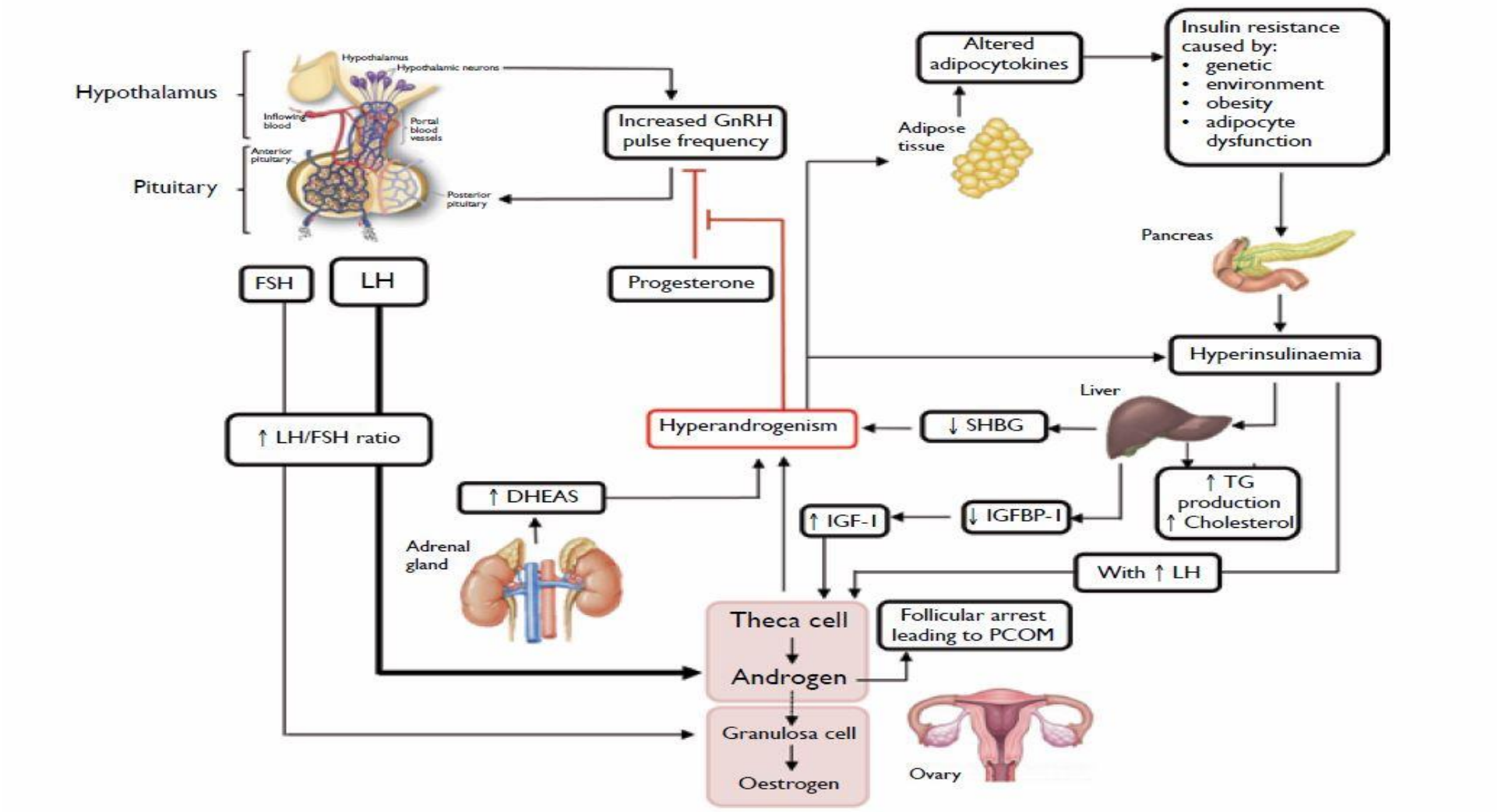

FIG 2. Pathophysiology of polycystic ovary syndrome
Abbreviations: DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; IGF-I = insulin-like growth factor I; IGFBP-I = insulin-like growth factor–binding protein-I; LH = luteinising hormone; PCOM = polycystic ovarian morphology; SHBG = sex hormone–binding globulin; TG = triglycerides

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PCOS

- There are no clear consensus guidelines on the diagnostic criteria for PCOS in adolescent girls within 2 years of menarche
- Most experts agree that longitudinal evaluation of symptoms such as acne, hirsutism, and oligomenorrhea should occur over the span of the first 1–2 years after menarche before establishing a diagnosis of PCOS.

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PCOS

- The clinical symptoms, including hyperandrogenism and chronic anovulation, typically develop during adolescence.
- Androgen excess is observed in approximately 60–80% of patients with PCOS, is a key feature of the disorder.
- the early onset of adrenarche may represent the initial clinical feature of PCOS for some girls.

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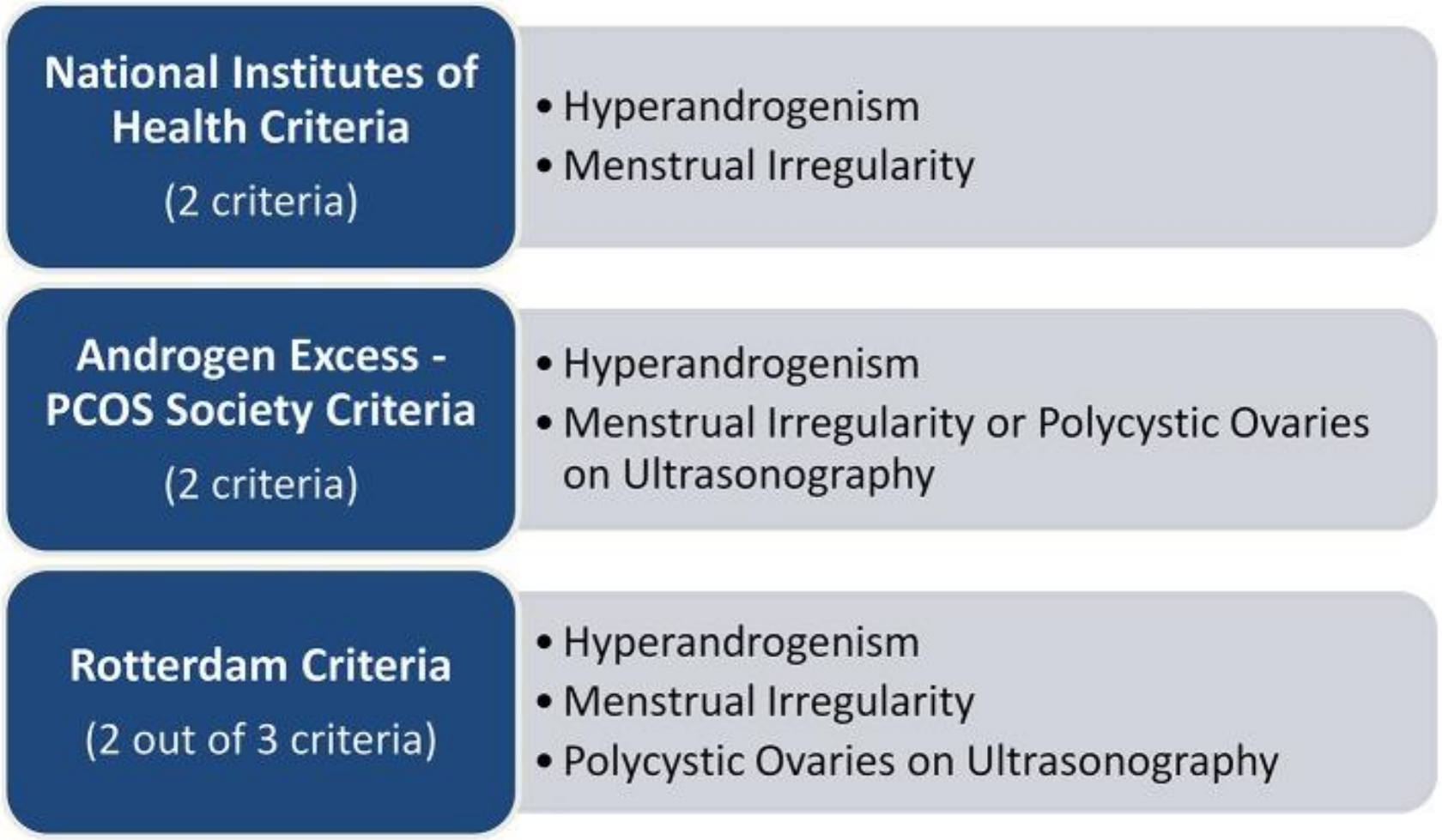
PCOS-Diagnostic Criteria



2-3 years after menarche

PCOS as a Metabolic Consequence

- Insulin resistance and hyperinsulinemia are common findings in women with PCOS independent of their degree of adiposity, body fat topography, and androgen levels
- Women with PCOS have a high risk of developing impaired glucose tolerance and type 2 diabetes mellitus
- The pathogenesis of IR in PCOS reflects the interaction of genetic influences, non-heritable intra- and extrauterine environmental factors, and alternative adaptations to energy excess.
- Puberty per se might play an important role in the molecular origins of IR and hyperinsulinemia. During puberty, adolescents experience a temporary decline in insulin sensitivity with a nadir in mid-puberty

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Treatment of PCOS

- No pharmacological treatment has been approved so far by FDA for use in adolescents with PCOS
  - some pharmacological interventions have been used to manage PCOS symptoms
- Weight loss and increased physical exercise are generally recommended as the first-line therapy in overweight or obese girls
  - Two small randomized controlled trials (RCTs) and one well-controlled clinical study in overweight PCOS girls have shown that the combination of weight loss and intensified exercise decreases testosterone levels and the free androgen index, increases SHBG concentrations, and normalizes menstrual regularity
  - The combination of lifestyle intervention with medications normalized androgen levels and menses in one of these studies

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Treatment of PCOS

- Metformin
  - only insulin sensitizer that has been evaluated in double-blind RCTs as single medication for adolescent PCOS
  - metformin use has increased over the last 10 years despite not being licensed for PCOS
  - A meta-analysis of metformin use with and without lifestyle changes in PCOS up to August 2014 showed beneficial effects on BMI and menstrual cycles
  - Observational studies and 6 randomized trials have demonstrated short-term beneficial effects of metformin in PCOS adolescents who were mostly overweight or obese.

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Treatment of PCOS

- Anti-Androgens:
  - Two types of anti-androgens are used in the management of PCOS
    - androgen receptor blockers like spironolactone, flutamide, and the third generation progestin, cyproterone acetate (not available in US)
    - inhibitors of 5-alpha reductase such as finasteride, which prevents the conversion of testosterone to DHT.
  - Spironolactone is the most commonly used because of its availability and safety profile, with an initial dose of 25 mg/day gradually increasing up to 200 mg/day.
    - At initiation, spironolactone may be associated with transient menstrual irregularity or spotting, breast tenderness, and occasionally fatigue or orthostasis from volume depletion.
    - Long term use reduces F-G score by 15-40% within 6 months of treatment
  - Flutamide is not available in some countries and is used sparingly because of concerns regarding its potential hepatotoxicity at high doses (>250 mg/day)
  - Anti-androgens significantly reduce hirsutism compared with placebo and normalize menstrual cyclicity better than monotherapy with metformin.
    - The efficacy is enhanced when combined with OCP or metformin

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Treatment of PCOS

- OCPs
  - Combination OCP containing an estrogen component (typically ethinyl estradiol) and a nonandrogenic progestin component address multiple concerns in adolescents with PCOS.
    - An increase in SHBG and decreased LH release due to the estrogen component leads to a decreased free androgen index, and the progestin component allows for suppression of endometrial proliferation and regular withdrawal bleeding.
  - Will improve hirsutism but may worsen LDL, total cholesterol, triglycerides, and insulin resistance
  - high-quality RCTs of specific OCP formulations for adolescents with PCOS are lacking to fully inform decision-making in this population

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Treatment of PCOS

- Combination Treatment
  - Provide the most effect treatments
  - Lifestyle modifications and use of metformin and anti-androgens

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Treatment of PCOS

- Local/cosmetic therapies
  - Photoepilation is the first-line management of localized hirsutism in PCOS.
    - Diode and alexandrite lasers are preferred

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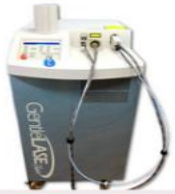
Lasers

IPL 	I II III	**Pros:** Customisable and approved for a broad range of skin types. Can target large areas quickly.	**Cons:** Not as effective as laser counterparts. May exacerbate hyperpigmentation.
Alexandrite 	I II III IV	**Pros:** Fastest system for laser hair removal. Ideal for treating larger areas. Works on thinner hair. Can treat light skin with freckles.	**Cons:** Can cause discolouration on individuals with darker skin tones.
Diode 	I II III IV V	**Pros:** Less risk of epidermal damage. Shorter recovery times. Faster treatment duration.	**Cons:** More painful than other lasers with slower repetitions. Less scientific research to back up long term effectiveness.
Nd:YAG 	I II III IV V VI	**Pros:** Safe for all skin types. Good for treating large areas. Able to treat vascular lesions.	**Cons:** Most painful of the lasers. Not as effective on fair skin or removing fine hairs. May require more treatments overall. Cosmetic Compare

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Rapid weight gain in the first 3 months of life does not predict obesity at 36 months in children born small for gestational age

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Introduction

Infants born small for gestational age (SGA) are at increased risk for obesity, insulin resistance, and cardiovascular complications.

Most studies indicate that excessive weight gain in the first 3 months of life confers an increased risk for obesity after five years of age. However, there are limited data about the natural history of weight gain and linear growth during infancy and childhood. Our study was designed to investigate patterns of growth in the first three years of life among patients born SGA.

Study Question

Is rapid weight gain in the first three months of life a predictor of obesity at 36 months of age?

Methods

Retrospective chart review of patients who were born SGA and who were followed either in the General Pediatrics Clinic or in the Pediatric Endocrinology Clinic at University of Miami Miller School of Medicine.

SGA was defined as a birth weight or length less than the 10th percentile for gestational age.

Data on weight and length from 1 to 36 months of postnatal age were collected.

Z scores for BMI were calculated using data files with Lambda Mu Sigma values from CDC. Overweight was defined as a Z score more than the 85th percentile.

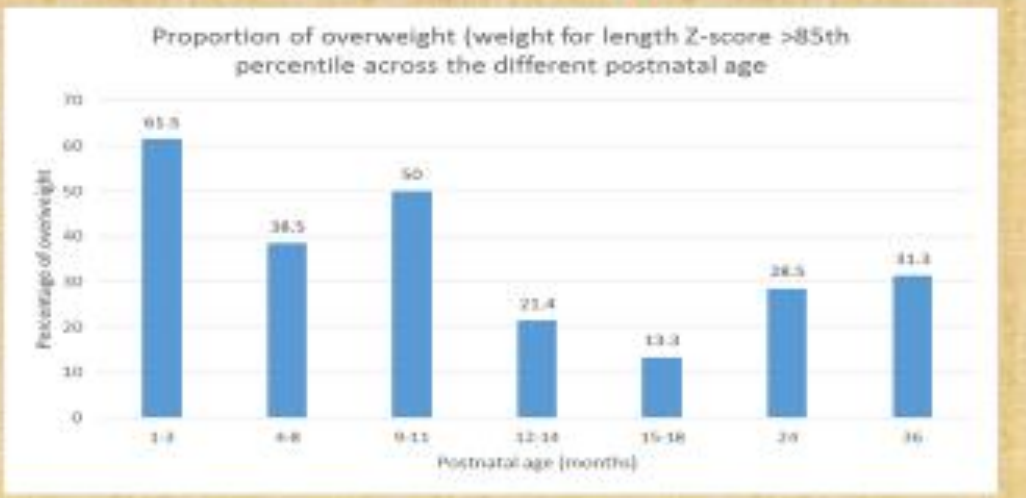
Data were analyzed by Fisher exact test for 2 x 2 table using Epi info (7.1.4.0) software.

Results

Twenty subjects were included in our study (60% male). The majority of subjects (61.5%) were overweight by the first three months of life.

At 18 months, 13.3% were overweight. At 36 months, 31.3% of children were overweight.

Overweight at 24 months was associated with overweight at 36 months (p value <0.01). However overweight at 3 months was not associated with overweight at 36 months (p value is 0.7).



Conclusion

Focus on the prevention of obesity has been strongly recommended by the American Academy of Pediatrics.

Our data are consistent with those of others indicating that most patients born SGA have rapid weight gain during the first 3 months. However, the early rapid weight gain did not persist and was not associated with being overweight at 36 months.

The correlation between overweight at 24 months and overweight at 36 months suggests that other factors contribute to the abnormal weight at 36 months among children born SGA.

References:

Milovanovic, I. et al. (2014) SGA children with Moderate Catch-up Growth Are Showing the Impaired Insulin Secretion at the Age of 4. PLOS ONE. June; 9 (6)
Lei et al. (2016) The Optimal Postnatal Growth Trajectory for Term Small for Gestational Age Babies: A Prospective Cohort Study. Journal of Pediatrics. January
Ezzahir et al. (2005) Time Course of Catch-up in Adiposity Influences Adult Anthropometry in Individuals Who Were Born Small for Gestational Age. Nature. Vol. 59 (2).
Marios et al. (2005) Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small or appropriate for gestational age children. Diabetologia. 48: 2605-2614

Nonclassical CAH

- Nonclassic congenital adrenal hyperplasia (NCAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene.
- Reported prevalence in women with androgen excess range from 0.6% to 9%
- Higher prevalences have been reported in Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations. Reported gene frequencies vary among ethnic groups and geographic region
- Treatment: hydrocortisone 7-16mg/m2/day divided every 8 hours

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Cushing's Syndrome

- Menstrual changes and/or hirsutism occur in approx. 70% of post-pubertal females but 2-4% of women with hirsutism have cushing's
- Impaired linear growth is a characteristic feature

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Other less common symptoms

Glucocorticoid Resistance

- Premature pubarche, hirsutism, oligomenorrhea, infertility, and hypokalemic hypertension.
- Autosomal dominant-due to loss of function mutation in the GCCR

Androgen Secreting tumors

- Elevated DHEA-S

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Summary

- Androgens are produced in the ovary, adrenal cortex, and by peripheral conversion
- Hirsutism has a scoring system and can be used to monitor treatment
- PCOS is the most common cause of hyperandrogenemia in adolescents
- PCOS is a multifactorial condition that requires combination treatments
- Other less common causes of hyperandrogenemia should be considered

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Merry Christmas and Happy New year!