Diagnosis and management of Polycystic Ovary Syndrome (PCOS) in adolescent girls

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Disclosure

Carolina Di Blasi, MD has no relevant financial relationships with ineligible companies to disclose.

Learning objectives

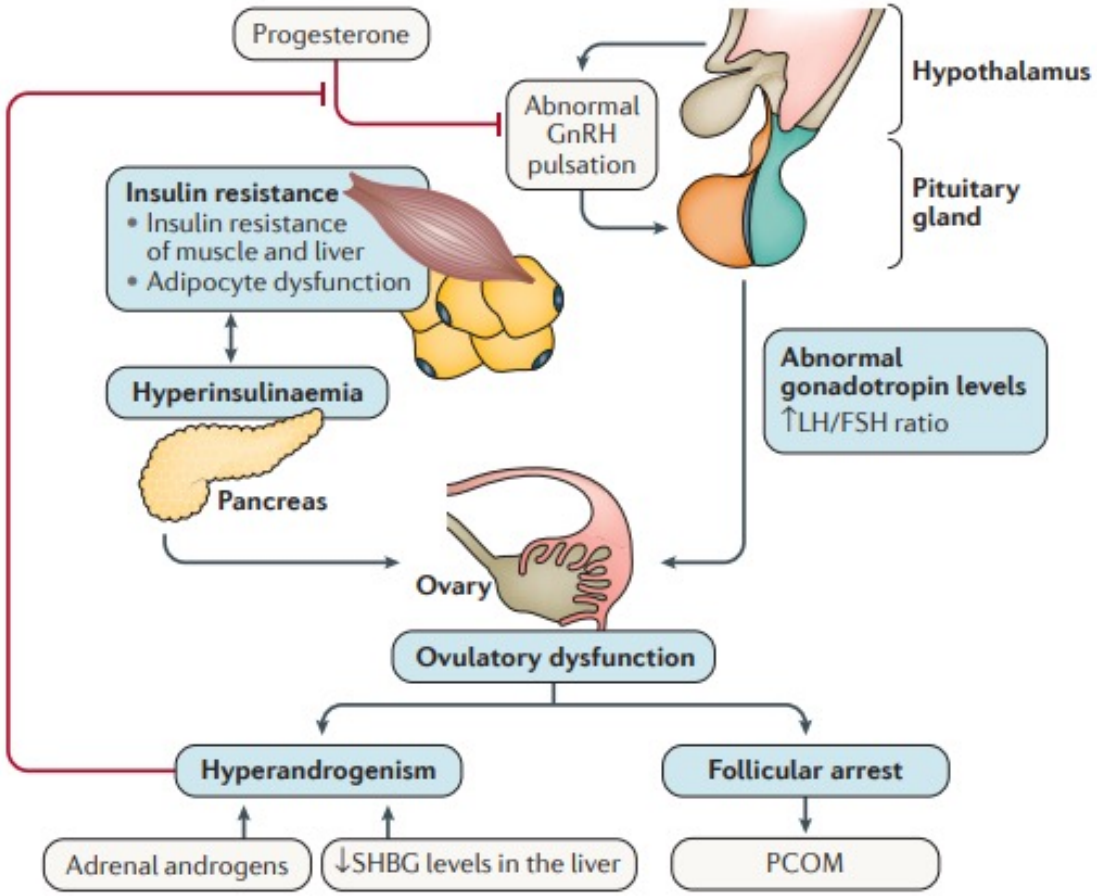
1. To review the **diagnostic criteria for PCOS**
2. To discuss the **diagnostic evaluation of PCOS**
3. To identify **medical care of PCOS**
4. Cases

Adolescents

PCOS

- Stein and Leventhal first described the disorder in 1935
- Common heterogeneous disorder
- Affects 6-15% of women of reproductive age
- Etiology is unknown
- PCOS is a multi-system disorder involving neuroendocrine, gonadal and metabolic components

PCOS



Azziz R, et al.Nat Rev Dis Primers, 2016

PCOS

Rotterdam consensus is now firmly grounded as the best evidence for adult women

Two of the following:

- **Oligo- or anovulation (MD)**
- **Clinical and/or biochemical hyperandrogenism (HA)**
- Polycystic ovarian morphology (PCOM)

AND exclusion of other etiologies

4 distinct phenotypes

A = MD + HA + PCOM (complete)

B = MD + HA (classic)

C = HA + PCOM (ovulatory)

D = MD + PCOM (non-androgenic)

PCOS

What are the appropriate diagnostic criteria for PCOS in adolescent girls? "Clinicians should be aware that the features of PCOS can overlap with normal puberty"

Adolescent girls can have:

- Irregular menses
- Acne
- Mildly elevated androgen concentration
- Multi-follicular ovaries on ultrasound

PCOS

Comorbidities of PCOS

- Irregular menses, infertility, hirsutism
- Impaired glucose tolerance
- Insulin resistance/hyperinsulinism
- T2DM
- Dyslipidemia
- Hypertension
- Endometrial cancer
- Obesity
- Nonalcoholic fatty liver disease
- Sleep apnea
- Depression and impaired quality of life
- Eating disorders and disordered eating

PCOS

What are the criteria for clinical evidence of hyperandrogenism in the adolescent girl?

- No consensus exists on the clinical criteria to reach the diagnosis of androgen excess in adolescents
- Androgen excess is considered
  - **Hirsutism**
  - **Severe inflammatory acne**

PCOS

Hirsutism

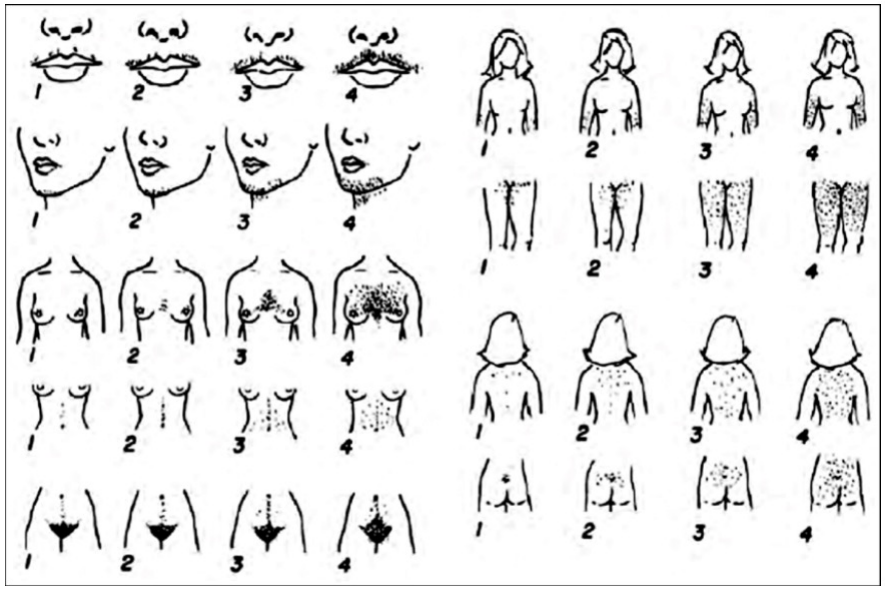
- Excess terminal hair growth in male-typical body areas
- Different from hypertrichosis: generalized increased body hair
- Interaction between circulating androgens, local androgen and the sensitivity of the pilosebaceous unit/hair follicle to androgens
- Severity of hirsutism does not correlate well with circulating androgen concentrations
- Hyperandrogenism can occur in the absence of hirsutism

PCOS

Modified Ferriman-Gallwey score

- Subjective nature
- Different cutoff among racial/ethnic groups

  ≥4-6 indicating hirsutism depending on ethnicity
- Terminal hair: >5 mm in length, pigmented, varying in shape and texture
- Patients may shave/use cosmetic treatments before their evaluation



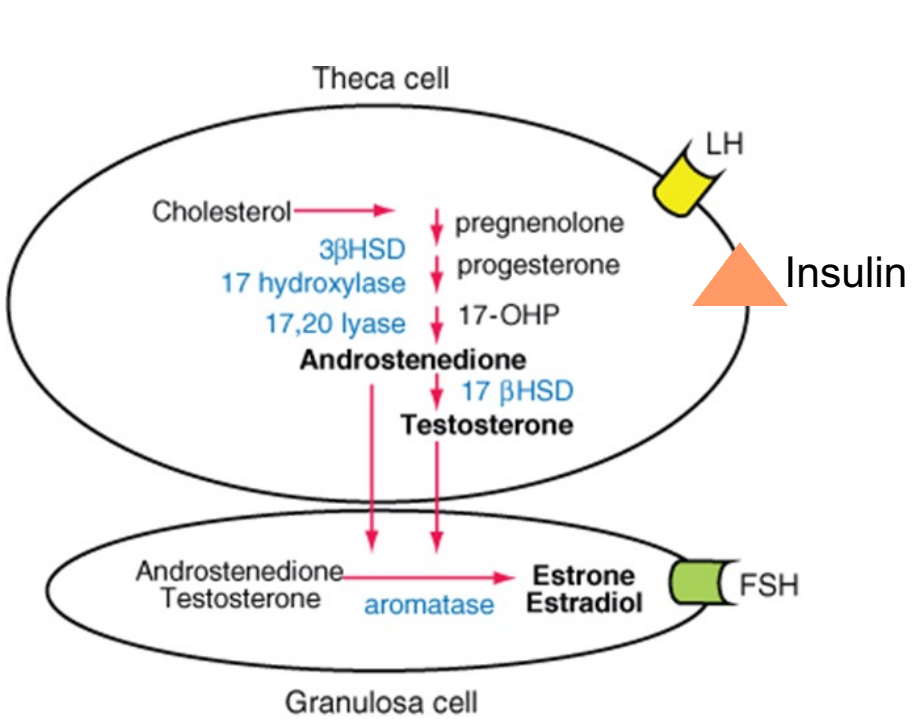
PCOS

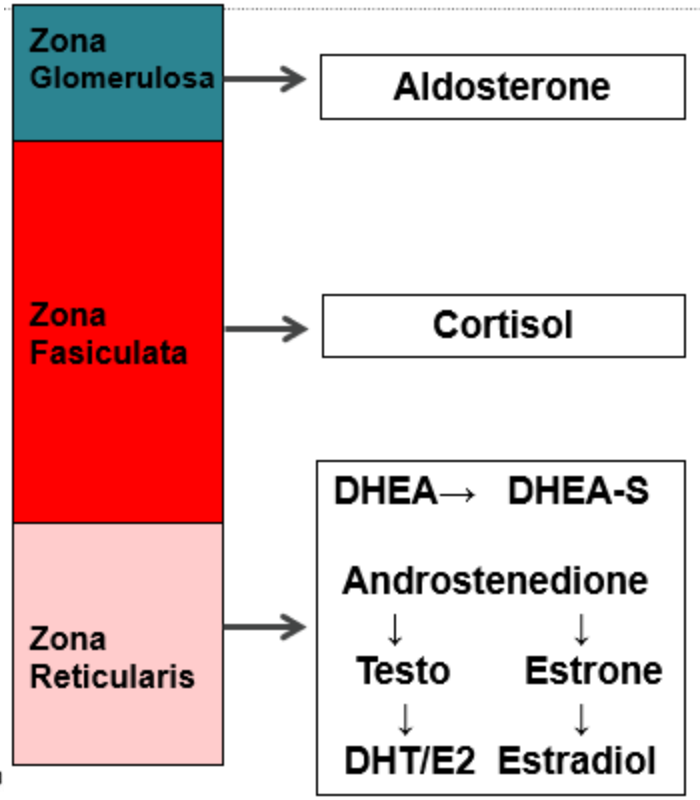
Acne Vulgaris

- Facial acne is very common in adolescents
- No universally accepted visual assessment tool exist
- **Severe acne** is usually resistant to topical treatment and antibiotics
- **Severe acne** is uncommon and may be associated with a hyperandrogenic endocrine disorder

PCOS

What are the criteria for evidence of biochemical hyperandrogenism in the adolescent girl?





Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

PCOS

- Testosterone is the major circulating androgen
- **Total/free T: most recommended hormonal determination to document hyperandrogenism**
- High quality assay GCMS and LCMS improve sensitivity/specificity but greater cost and decreased availability
- No cut-offs recommended, should be based on lab reference
- **Persistent elevation**
- If a patient is on COCP→ **3-months wash-out period** is recommended before testing
- Other androgen elevations provide limited additional information in diagnosing PCOS but may be use in ruling out other conditions

PCOS

What are the criteria for evidence of Oligo/Anovulation in adolescents?

- Median age at menarche 12-13 years, has remained relatively stable
- Many adolescent girls with irregular menstrual cycles are ovulating
- Ovulatory dysfunction can still occur with regular cycles

PCOS

Irregular menstrual cycles

- **Defined according to years post-menarche**
- Normal <1-year post-menarche
- >1 to <3 years post-menarche: <21 or >45 days,
- >3 years post-menarche to menopause: <21 or >35 days, <8 cycles/year
- >90 days for any one cycle (>1-year post-menarche)
- Primary amenorrhea by age 15 or >3 years post thelarche

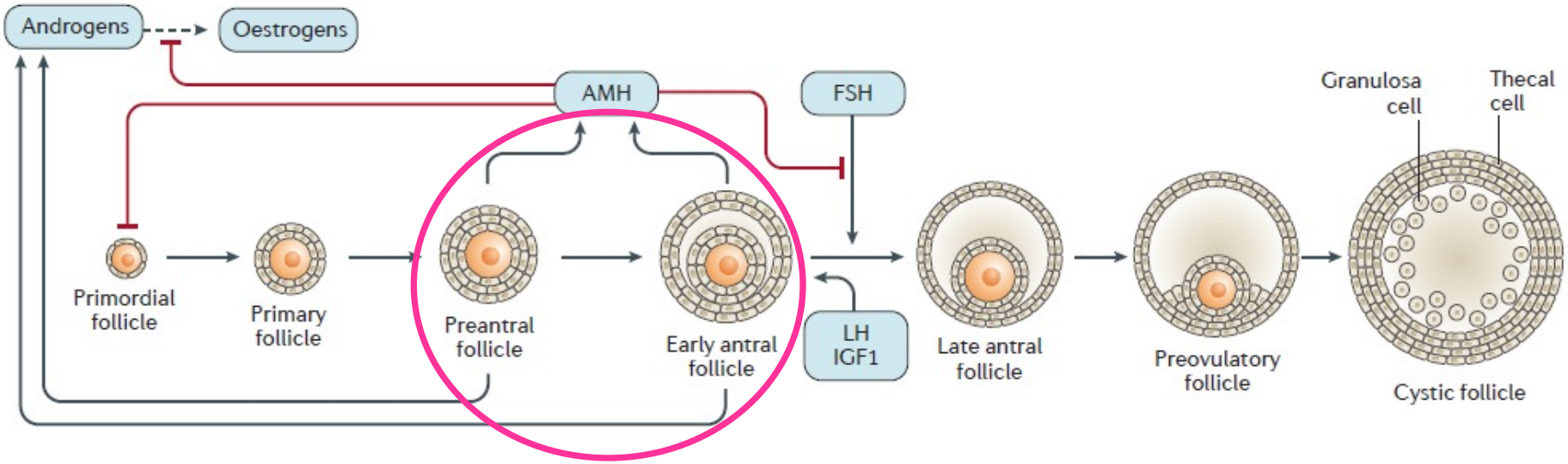
PCOS

Challenge for the clinician

- To differentiate “physiologic adolescent anovulation” from those with true ovulatory dysfunction
- The persistence of oligomenorrhea (MC >45 days), secondary amenorrhea (no MC >3 months) or amenorrhea in girls with complete pubertal development suggest the coexistence of androgen excess

PCOS

What are the criteria for PCOM in an adolescent girl?



Azziz R, et al.Nat Rev Dis Primers, 2016

PCOS

- **Ultrasound should not be used for the diagnosis of PCOS in those with gynecological age <8 yrs (8yrs after menarche)** due to high incidence of multi-follicular ovaries in this life stage, and the natural growth of the ovary
- PCOM, variously defined, has been reported with a prevalence of 30-40% in healthy girls
- PCOM is an inconsistent finding and does not predict the development of PCOS
- Transvaginal approach is preferred in sexually active females (bandwidth 8MHz): follicle number per ovary ≥20 and/or ovarian volume ≥10 ml

PCOS

AMH

- Produced by small ovarian antral follicles
- AMH declines with selection of the dominant follicle
- AMH provides valuable information regarding ovarian reserve
- Can be a possible surrogate to PCOM?
- Technical issue with the assay

PCOS

What diagnostic procedures are appropriate in adolescents to exclude other causes of hyperandrogenism and amenorrhea?

- Late onset CAH → the most common form is 21-hydroxylase deficiency due to mutation in the CYP21A2. Prevalence 1: 1000 (↑ in certain ethnic groups)
- Thyroid dysfunction
- Hyperprolactinemia
- Ovarian/adrenal androgen secreting tumors
- Cushing: pituitary adenoma, primary pigmented nodular adrenocortical disease, GC resistance

PCOS

LABS

- 17-OHP: Late onset CAH
  Morning 17-OHP > 200 mg/dL
  ACTH-stimulated 17-OHP >1500-10000 mg/dL
- Total and free testosterone
- SHBG
- Androstenedione
- DHEAS
- TFTS, PROL, LH/FSH

PCOS

What is the role of Insulin Resistance/Hyperinsulinemia in the diagnosis of PCOS in adolescents?

- **Insulin resistance in the liver, muscle and adipose tissue** → ↑ insulin secretion.
- Skin, steroidogenic tissues, hypothalamus retain insulin sensitivity
- **Insulin** → ↓ **SHBG**
- **The insulin resistance of PCOS is inherent to the syndrome** and is over and above the conferred by obesity
- Intrinsic to PCOS in lean or obese
- Insulin plays a role in the stimulation of ovarian androgen production

PCOS

What prenatal factors are relevant for PCOS?

- Low birth weight is associated with impaired glucose tolerance, T2DM, and CVD
- IUGR and low birth weight with rapid postnatal growth → premature pubarche and PCOS

PCOS

Does the diagnosis of PCOS during adolescence provide an opportunity for meaningful intervention? What are the risks of over diagnosis?

- Timely diagnosis of PCOS leads to awareness
- Provides an opportunity for a meaningful intervention: healthy lifestyle counseling, testing for comorbidities or medical treatment

- Overdiagnosis can lead to overuse of metformin and OCP → metanalysis have shown that the medications commonly used in the treatment of PCOS have a low risk of severe adverse effects
- Overdiagnosis can lead to unnecessary labeling and unwarranted interventions, impact an adolescent's quality of life, creating unnecessary anxiety

PCOS

Treatment

- **Individualized and chosen to optimize symptom relief**
- "Discussion and encouragement of appropriate dietary and exercise interventions"
- Cosmetic treatments

  Waxing, bleaching and topical 13.9% eflornithine cream

  Permanent cosmetic treatments: electrolysis and laser hair removal (deferred until androgen levels are decreased)

PCOS

COCPs

- First line therapy (skin features improve)
- ↓ androgens, ↑ SHBG, normalize menses, prevent pregnancy, protect the endometrium. In adults: ↑ T Chol, HDL and TG
- COCPs no changes in glucose tolerance or weight
- COCPs:

  EE 20-35 mcg tab

  Synthetic progestogens: vary in their androgenic activity

  Newer ones: desogestrel, gestodene and norgestimate (Ortho-cyclen) have low androgenic activity. Dienogest, cyproterone acetate and drosperidone (Yaz) have antiandrogenic activity
- Both estrogen and progestin → ↑ risk of VTE (↑ E2 doses)
- Family history of VTE or thrombophilia needs to be ascertained

PCOS

Metformin

- Improve insulin sensitivity → ↓ insulin production
- Decrease androgen concentration → improve ovulatory function
- No effect on hirsutism
- Should be used primarily in girls with IR/H

Antiandrogens

- 2nd line for hirsutism
- **Spironolactone**, flutamide, finasteride
- Reduce growth of new terminal hair
- Highly effective birth control must be used simultaneously
- Hyperkalemia with spironolactone
- Hepatotoxicity with Flutamide

PCOS

Key points

- Adult criteria is not applicable for adolescent girls
- PCOS is a diagnosis of exclusion
- The diagnosis of PCOS in adolescents should be primarily based on clinical and/or biochemical signs of hyperandrogenism and irregular menses
- Diagnosis should be deferred until at least 2 years following menarche
- If not fulfilling this criteria: “at risk for PCOS”
- Features of PCOS overlap normal pubertal development. Hence, caution should be taken before diagnosing PCOS without longitudinal evaluation

PCOS

Key points

- PCOM may be observed, but is not criteria
- Obesity, IR/H are common comorbidities
- Treatment may be indicated even in the absence of a definitive diagnoses

Case 1

13 9/12 Caucasian female

Referral: Evaluation of possible PCOS

Clinical History

- Family main concern was weight gain over the last few years
- No changes on physical activity or food intake
- Thelarche: 9 yo
- Menarche:13 7/12 yo, only one menstrual cycle
- Oily skin and acne
- No hirsutism
- Frequent skin infections and sinusitis

ROS

- Fatigue, decreased muscle strength

Case 1

Family History

- Mother: obesity and hyperlipidemia, 162 cm (5f 4in), initiated menarche at 12
- Father: obesity, depression, GERD, OSA on CPAP, kidney and gallbladder stones, 172 cm (5f 8in)
- MPH: 161 cm (5f 4in): 25-50%
- 2 healthy and lean brothers

Diet: No recent changes

- She drinks juice, sweet iced tea and almond milk
- Pays attention to portion size

Activity

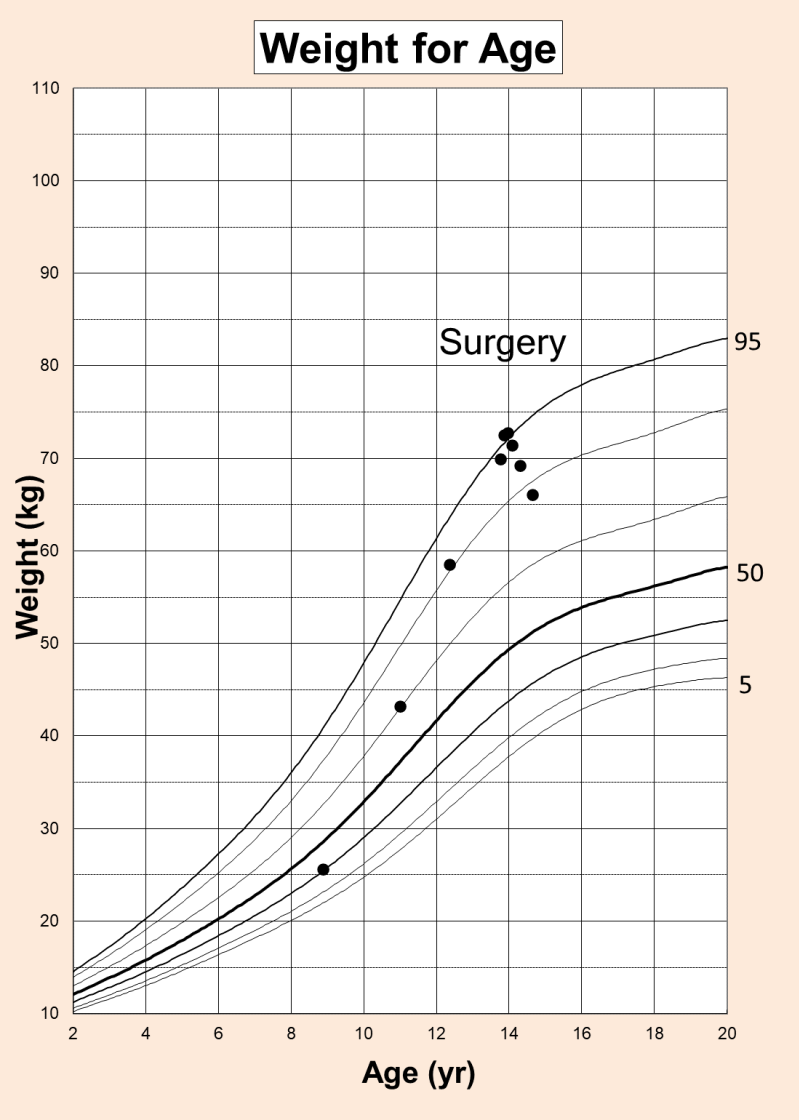
- School PE 4x/week, volleyball
- Straight A student

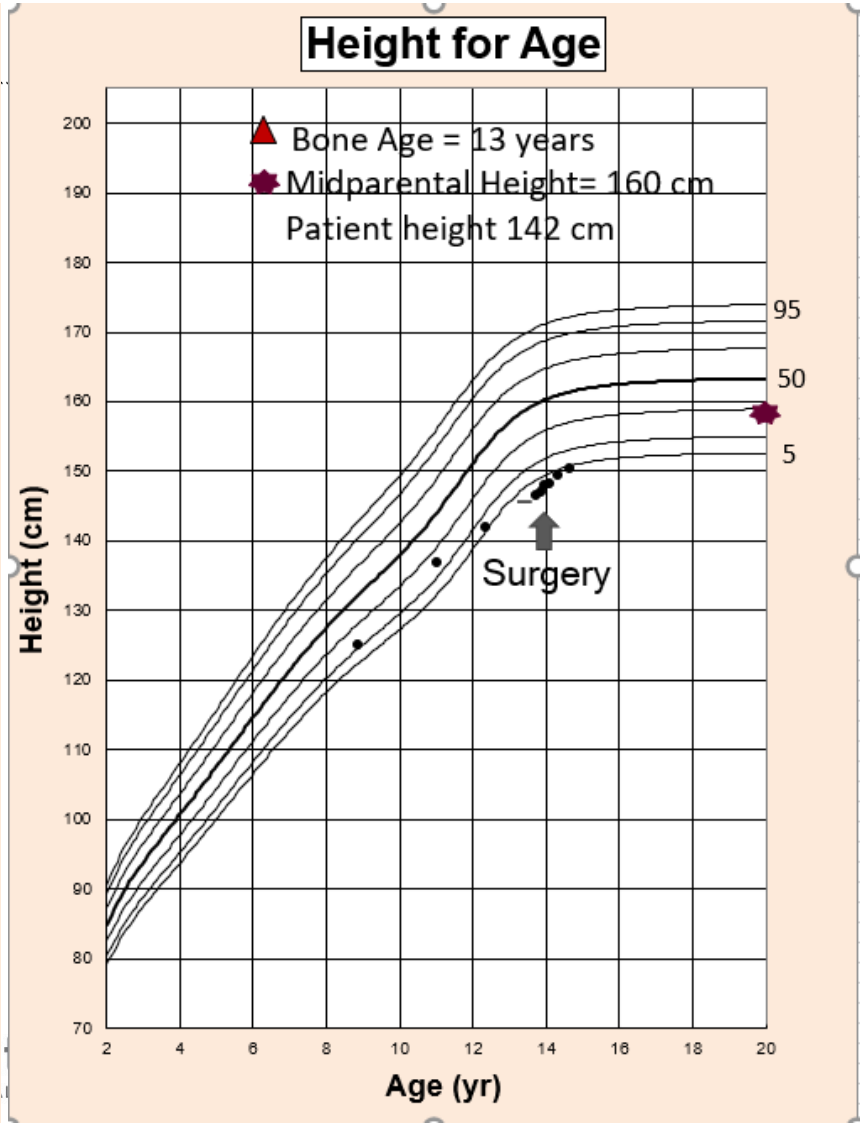
Case 1

Physical Exam

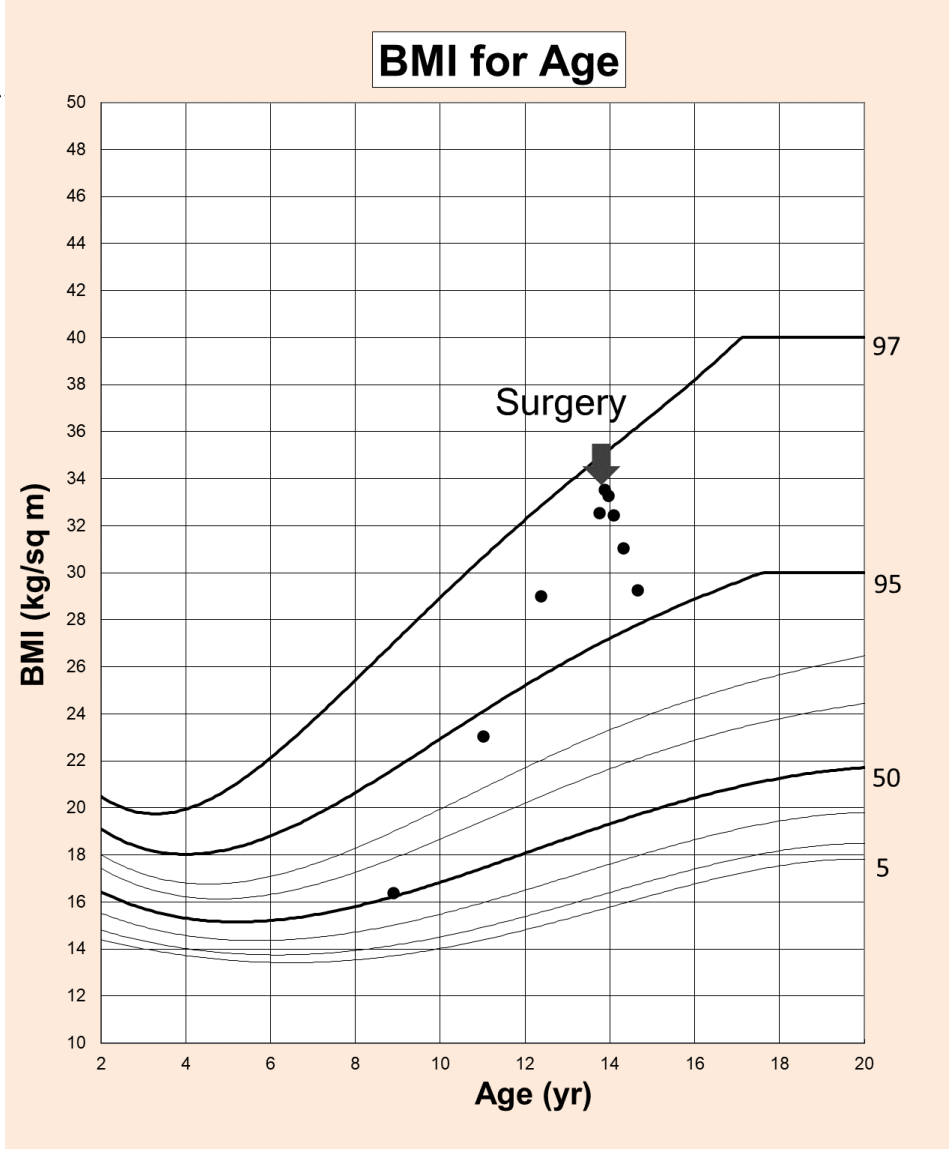
- HR 97, BP 127/61 **(SBP 95-99%)**
- General: Proportionally obese, No dysmorphic features
- HEENT: Normal eye exam, normal peripheral vision
- Neck: normal thyroid gland
- CV: normal. Resp: normal
- Abdomen: obese, no HSM, no masses
- Breast: Tanner 4; PH: Tanner 4, no clitoromegaly
- Skin: facial and upper thorax **acne** and **oily skin**. **Striae** on her abdomen , flank and arms, dark pink. Slight skin hyperpigmentation?. **Acanthosis nigricans** on the back of the neck and armpits. **No hirsutism**
- Neuro: **Normal proximal muscle strength**
- Skeletal: no cubitus valgus, no nail bed hypoplasia, no Madelung deformity, no brachydactyly

Case 1


Weight for Age
Weight (kg)
Age (yr)
Surgery
95
50
5


Height for Age
Bone Age = 13 years
Midparental Height= 160 cm
Patient height 142 cm
Height (cm)
Age (yr)
Surgery
95
50
5

Case 1



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Case 1

- 17-OHP 78 ng/dL, DHEAS 226 mcg/dL (31-233), Testosterone 71 ng/dL (tanner IV: 20-75), free testosterone 2.1 ng/dL. LH 3.1 mIU/mL, FSH 3.9 mIU/mL, estradiol 50 pg/mL.
- Random Cortisol (12pm) 10.9 mcg/dL, ACTH (12 pm) 82 pg/mL (normal a.m: 10-60).
- Midnight salivary cortisol x2: 296 and 3760 ng/dL (normal <100)
- 24-hour UFC 80 mcg/24hs (BSA=1.69, =47.3 mcg/m2/24 hours)
- 1mg Dexamethasone suppression test: morning Cortisol 7.2 mcg/dL (normal <1.8)
- 8 mg Dexamethasone suppression test: morning Cortisol 1.2 mcg/dL (87% suppression from baseline of 9.3 mcg/dL), consistent with ACTH-dependent Cushing.
- Brain MRI: 3 mm lesion within the superolateral portion of the pituitary gland Pituitary stalk was subtly deviated towards the right indicative of mass lesion.

Case 2

18 yo F presented to established care at SCH-Adolescent medicine

Relocated from Nevada to Washington

Diagnosed at 11 yo PCOS

Gynecologic history

- Thelarche 9 yo, adrenarche 10 yo
- Menarche at 11 yo, subsequent oligomenorrhea
- She had one period, and none again until she was started on OCP

Other clinical features she reported:

- Hirsutism: hair on face, chest and back. She shaves frequently
- Acne on chest, shoulders and back.
- Occasional right lower quadrant pain.

Treated since the age of 11→17 yo : COCP, Spironolactone and Metformin

Off medications for 1 year, without spontaneous resumption of menses. Hirsutism worsened. **Initial diagnostic evaluation????**

Case 2

Physical Exam

BP 136/78, HR 64, other visits 140/82, 123/76

Obese and Tall

Masculine features

Weight: 110.2 kg (99%), Height 174.5 cm (96%), BMI 36.19 kg/m2 (98%)

Skin: Acne with papules, hair across upper lip, chin, abdomen, dark chin pigmentation, acanthosis nigricans, no striae

Normal neck exam

Abdomen: soft, non-tender, non-distended, no organomegaly, no masses

Breast Tanner stage V

GU: Pubic hair Tanner V, Clitoris: 2 cm in length and 1 cm in width

Small vaginal introitus. No internal examination

Case 2

LABS	
Hemoglobin A1C	5.8%
Urine bHCG	Negative
Glucose	91 mg/dL
AST	31 IU/L
ALT	**51 IU/L**
TSH	0.89 mcIU/mL
17OH-Progesterone (morning)	**1261 ng/dL (36-200)**
DHEAS	202 mcg/dL
Testosterone Total LC/MS	**359 ng/dL (10-60)**
Testosterone Free LC/MS	**14 ng/dL (0.3-1.9)**
FSH	2 mIU/mL
Prolactin	12 ng/mL

Case 2

- **Provera challenge: Medroxyprogesterone 10 mg for 10 days → assessment of estrogen status and outlet obstruction:** She did not bleed

LABS	
Glucose	89 mg/dL
Estradiol	16 pg/mL (Tanner V: 22-370)
Insulin level (fasting)	**25.5 mcIU/mL (<17)**
IGF1	589 ng/mL (147-842)
IGFBP3	5.7 ug/mL (2.7-8.9)
Karyotype	46,XX

Case 2

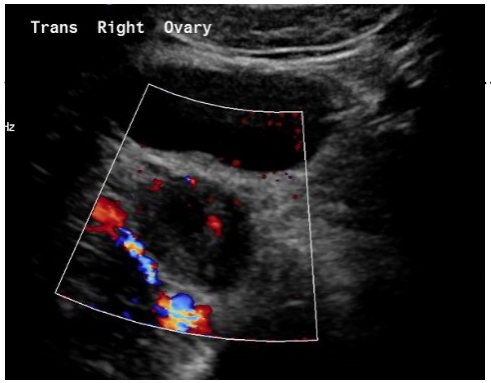
Cosyntropin stimulation Test		
	Baseline	**Post stimulated**
Cortisol (mcg/dL)	25	13
11-Deoxycortisol Specific (ng/dL)	54	27
Deoxycorticosterone (ng/dL)	14	9.7
17OHProgestone (ng/dL)	**877**	**1270**
17OHPregnenolone (ng/dL)	**970 (53-357)**	447
DHEA (ng/dL)	**1220 (160-800)**	848
Testosterone Total (ng/dL)	**349 (10-60)**	427
Androstenedione (ng/dL)	**535 (50-224)**	566
Progesterone ng/dL	118	130

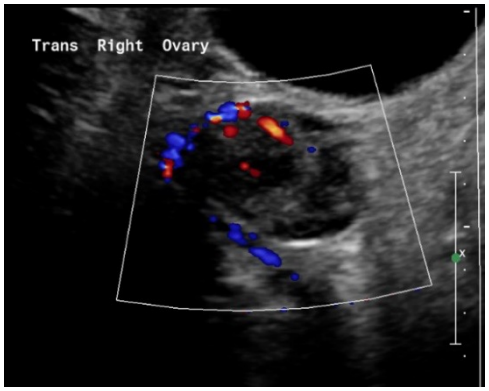
Case 2

Genetic Testing:
Negative for common mutations of CYP21A2, the 21-Hydroxylase gene

LABS	
ACTH (pg/mL)	14
Midnight Salivary Cortisol (ng/dL)	<50 (<100)

Case 2





Pelvic Ultrasound

Right Ovary: 4.8 x 3 x 3.3 cm, volume 24.4 mL.
3.6 x 2.5 x 2.1 cm, volume 9.6 mL, complex cyst, with sonographic characteristics of a corpus luteum cyst with hyperechoic periphery and hypoechoic central region
Left Ovary: 3.9 x 2.3 x 2.3 cm, volume of 10.5 mL, normal morphology
Adrenal glands appeared normal

Repeat Ultrasound 3 weeks after
Right Ovary: 4.4x 4.3x 2.5, volume 24.8 mL
Right ovarian cyst: 2.9x 3.4x 1.9 cm, volume 10 mL
Left Ovary 2.5x 3.6x 1.6 cm, 7.5 mL volume
No Changes

CT pelvis and Abdomen 4 weeks after

- No adrenal tumors. The right Ovary shows a 3.2x 2.0x 2.8 cm hyperenhancing lesion with central hypodensity. Given lack of regression after 10-14 days in a nongravid patient, cyst was present for 8 weeks, stromal or sex cord tumor are considerations

Case 2

- She was operated via laparoscopy
- Intra-op genital exam revealed a clitoris 4 cm in length and 1 cm in width
- Right salpingo-oophorectomy
- Negative peritoneal cytology
- Alpha Feto Protein-Tumor: Negative

STEROID CELL TUMOR, NOT OTHERWISE SPECIFIED
OVARIAN CHANGES CONSISTENT WITH CHRONIC ANOVULATION

Case 2

LABS		
	2 weeks after surgery	**4 months after surgery**
17OH-Progesterone (ng/dL)	<15 (before ~1200)	
DHEA (ng/dL)	352 (before 1220)	
DHEAS (mcg/dL)		211
Testosterone (ng/dL)	40 (before >300)	28
Free Testosterone (ng/dL)		1.0
Androstenedione (ng/dL)	145	
Estradiol (pg/mL)	23	
Inhibin A (pg/mL)	4.5 (<97.5 premenopausal)	6.3
Inhibin B (pg/mL)	49 (<139 premenopausal follicular, <92 premenopausal Luteal)	64

PCOS

Key References

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PCOS

Thank you!