Polycystic Ovary Syndrome (PCOS)

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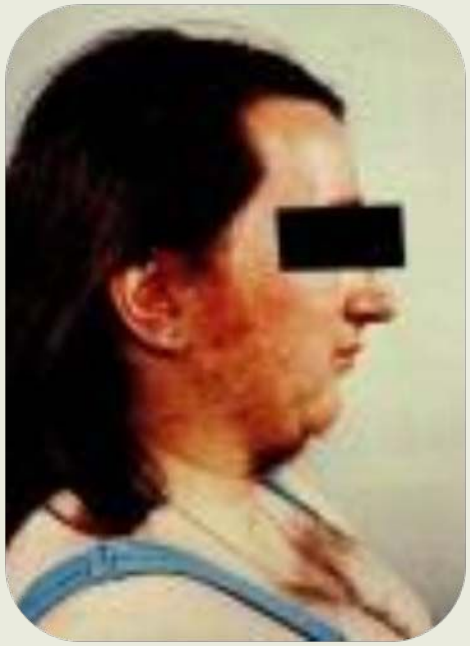
LA1 -163 (1)

Objectives

1. Describe PCOS and associated pathophysiology
2. Identify risk factors of and conditions related to PCOS
3. Diagnose and evaluate comorbidities relevant to PCOS
4. Characterize goal specific therapy options

Polycystic Ovary SYNDROME

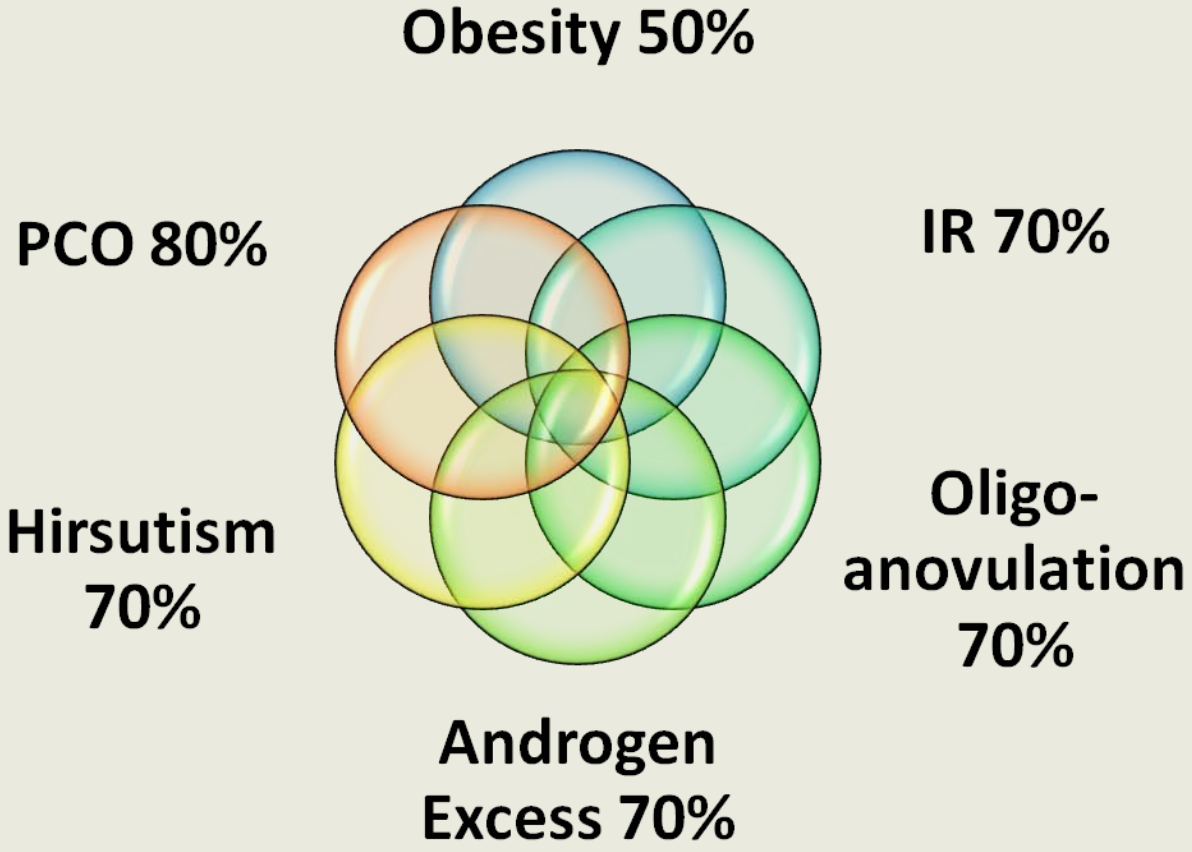
- 1800s: polycystic ovaries
  - "cystic oophoritis"; "sclerocystic"
- Stein & Leventhal (1953)
  - Enlarged ovaries, hirsutism, obesity, and chronic anovulation
- "Syndrome O"
  - Ovarian confusion
  - Ovulation disruption
  - Over-nourishment
  - Overproduction of insulin



PCOS

- Collection of signs and symptoms
- May be difficult to diagnose
  - Heterogeneous presentation
  - Features change with age
- NO single test or feature is diagnostic

PCOS: Clinical Presentation Signs and Symptoms



Epidemiology

- Most common endocrine abnormality in reproductive aged women

- 5-15% women affected – with ethnic predilection
  - Caucasians: 4.8
  - Latina/hispanics: %
  - African americans: 13% 8.0
- Hereditary: %
  - Affected mother 35%
  - Affected sister 40%

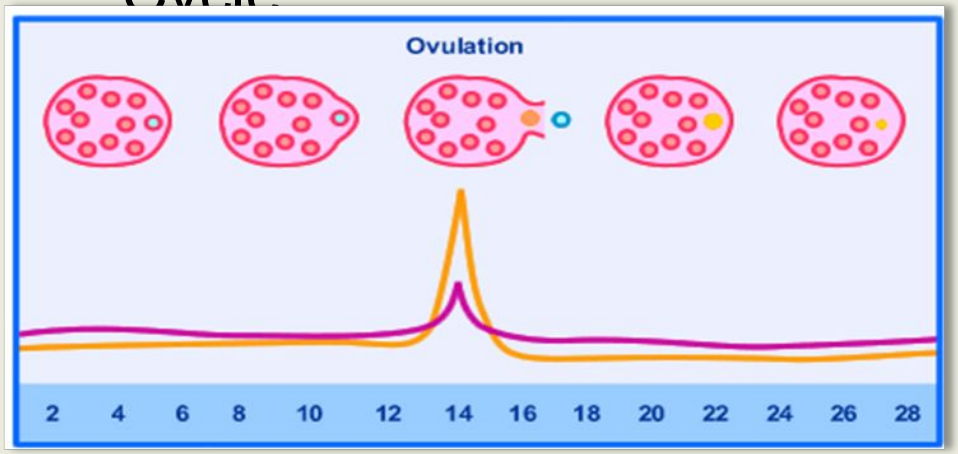
Polycystic Ovary Syndrome (PCOS)

ETIOLOGY & PATHOPHYSIOLOGY

PCOS: Etiology

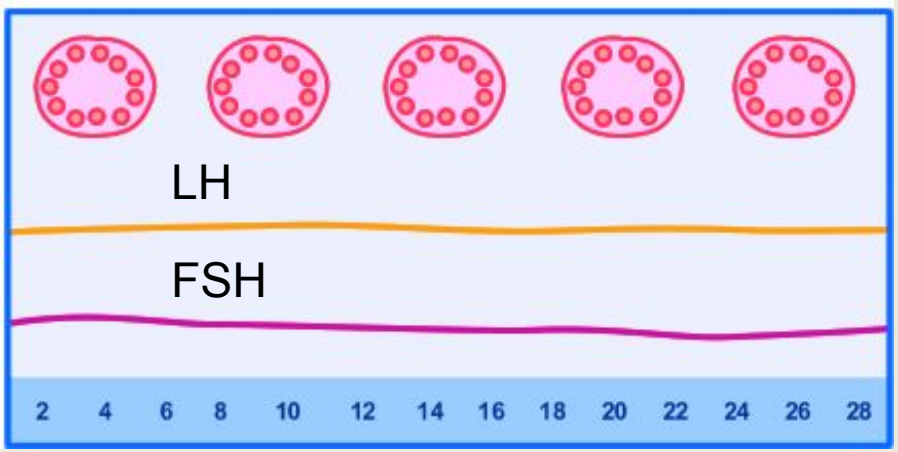
- Neuroendocrine derangement: ↑LH relative to FSH
- Hyperinsulinemia: defect in insulin action or secretion
- Androgen excess: ovarian and adrenal

Normal Menstrual Cycle



Cycle day

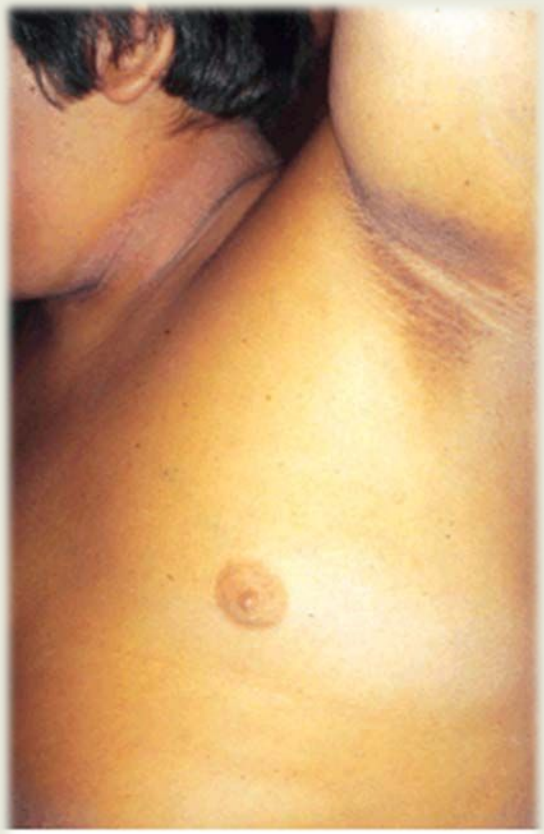
PCOS



Cycle day

Effects of Hyperinsulinemia

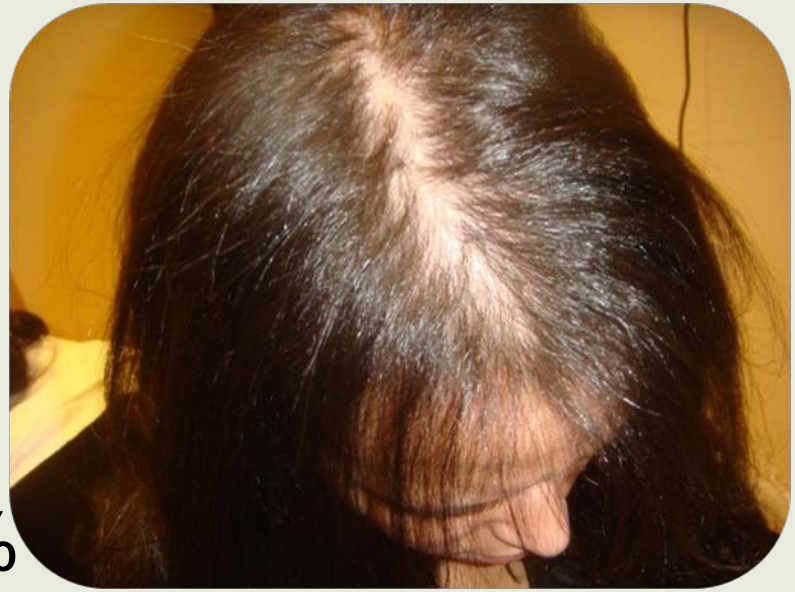
- Decrease binding proteins (ie., SHBG, IGFBP-I)
- Increase unbound androgens
- Reduce HDL [good] cholesterol
- Risk for PCOS (Legro et al.,1999; Dunaif, et al. 1997)
  - Insulin resistance: ~50%
  - NIDDM: 8%
- Acanthosis nigricans



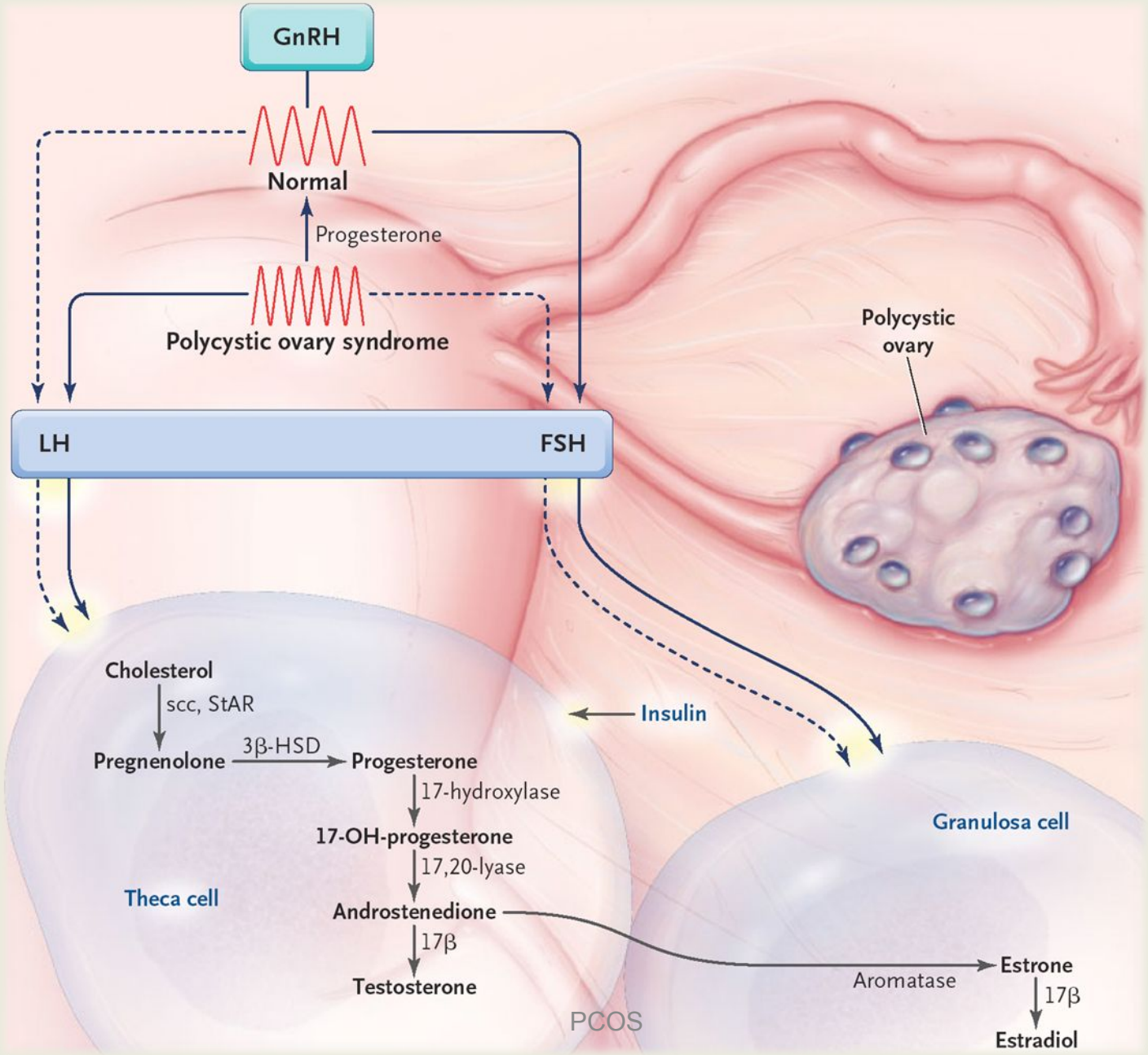
Acanthosis nigricans Classic hyperpigmented axillary lesion in acanthosis nigricans. Courtesy of Jeffrey Flier, MD.

PCOS: Androgen Excess

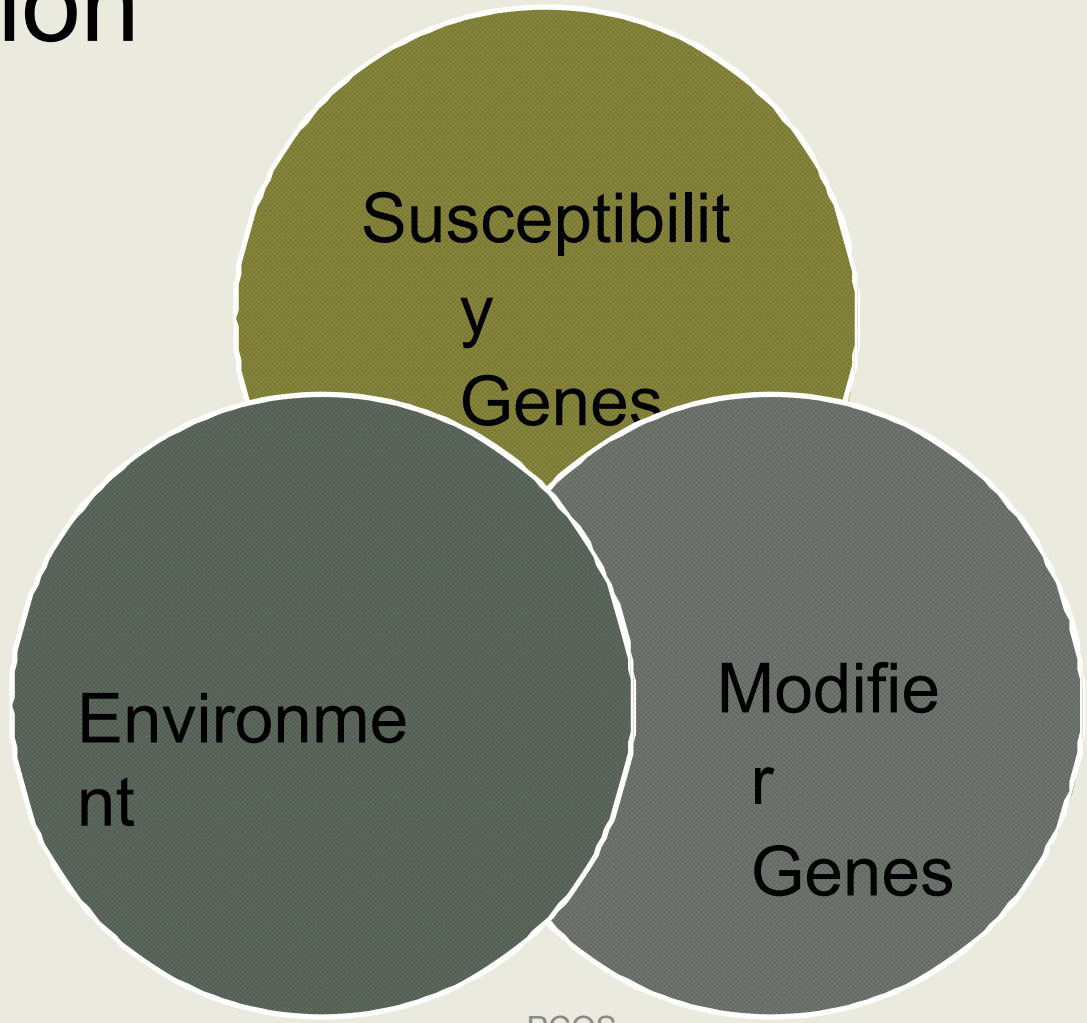
- Worse with hyperinsulinemia
- Hirsutism: 80% PCOS
- Acne: 20% PCOS
- Androgenic alopecia: 10% PCOS



PCOS Etiology: Unifying theory?



PCOS: Phenotypic & Genetic Variation



Gene	Polymorphism	Phenotype
IGF-2	*Apa*I	PCOS
IGF-IR	Trinucleotide repeat	Increased fasting glucose and insulin resistance
PPAR-γ2	Pro12Ala	Body mass index
		Lower insulin resistance
		PCOS
		Obesity
		Lower insulin resistance and hirsutism score
Paraoxonase (PON-1)	-108C/T	PCOS
	Leu55Met	Obesity and insulin resistance
SORBS1	Thr228Ala	Obesity
Calpain-10	UCSNP-43,-19,-63	PCOS and insulin levels
	UCSNP-43,-45	Hirsutism score and idiopathic hirsutism
	UCSNP-44	PCOS
Adiponectin	45 T/G	Androstenedione
		PCOS
		Insulin resistance
	276 G/I	Obesity and insulin resistance
		Lower adiponectin levels

Adapted from Luque-Ramirez et al, Clinica Chimica Acta, 2006.

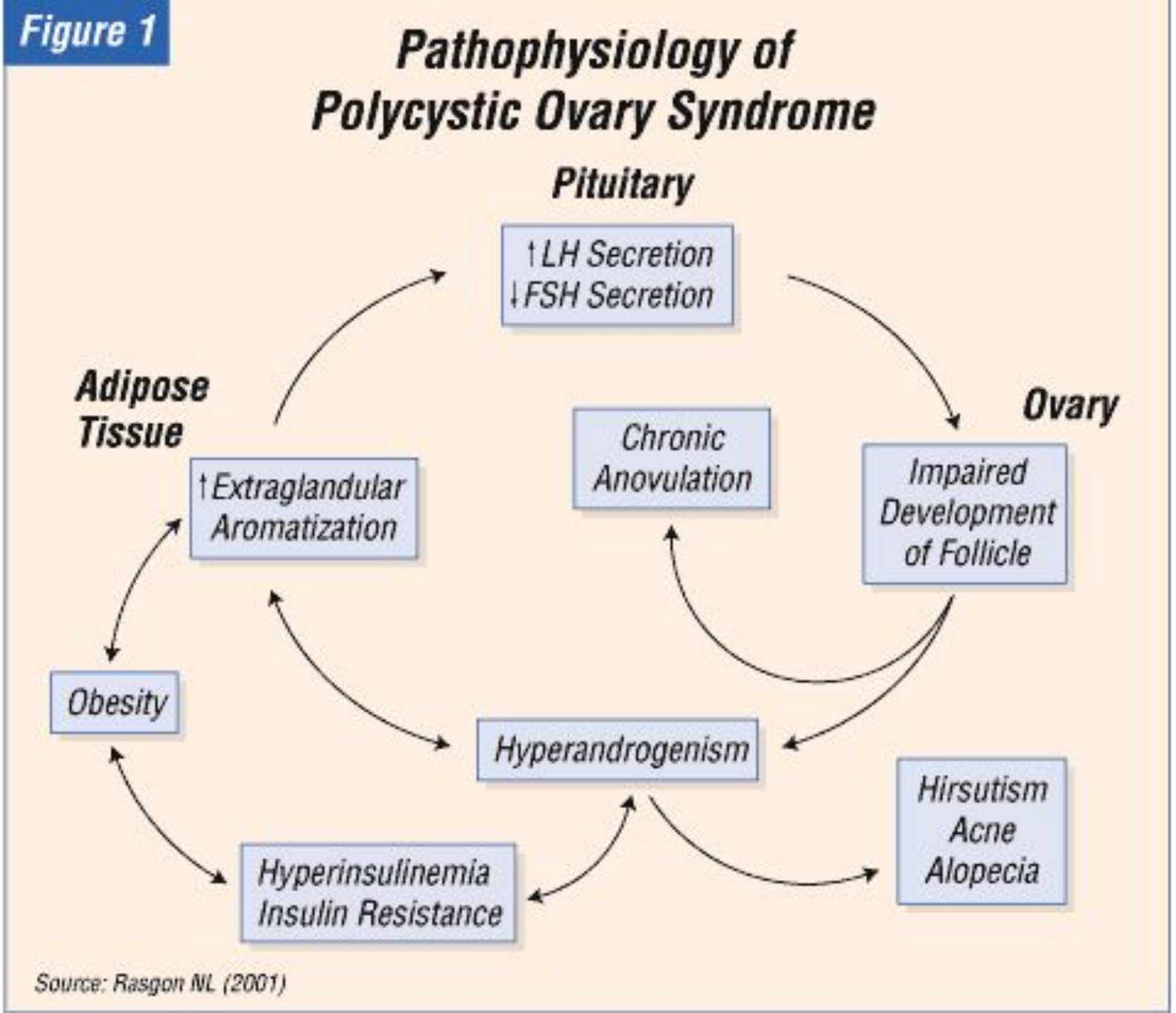


Figure 1
Pathophysiology of Polycystic Ovary Syndrome
Pituitary
↑LH Secretion
↓FSH Secretion
Adipose Tissue
Ovary
↑Extraglandular Aromatization
Chronic Anovulation
Impaired Development of Follicle
Obesity
Hyperandrogenism
Hirsutism
Acne
Alopecia
Hyperinsulinemia
Insulin Resistance
Source: Rasgon NL (2001)

PCOS: Diagnostic Criteria

- NIH/NICHD: USA, 1990
- ESHRE/ASRM: Rotterdam, 2004
- Androgen Excess-PCOS Intl Society: 2006

PCOS Criteria

NICHD/NIH Definition, 1990

Less inclusive

1 and 2 needs to be met:

1. Hyperandrogenism
   - clinical (hirsutism, acne, frontal balding)
   - biochemical (high serum androgen concentrations)
2. Menstrual irregularity
   - Chronic anovulation
   - Oligomenorrhea, > 35d

Rotterdam Definition, 2004

More inclusive

2 of 3 need to be met:

1. Hyperandrogenism
   - Clinical or biochemical
2. Menstrual irregularity
3. **Polycystic ovaries **

   (Key difference from NIH)

FOR BOTH: Exclude other causes (hyperprolactinemia, NC-congenital adrenal hyperplasia, thyroid disorder, etc.)

AE-PCOS Society, 2006

- **Hyperandrogenism****: Hirsutism and/or hyperandrogenemia

AND

- Ovarian Dysfunction: Oligo-anovulation and/or polycystic ovaries

- Exclusion of other androgen excess or related disorders

ACOG
PRACTICE
BULLETIN
CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

Number 108, October 2009(Replaces Practice Bulletin Number 41, December 2002)

Table 1. Recommended Diagnostic Schemes for Polycystic Ovary Syndrome by Varying Expert Groups

Signs and Symptoms*	National Institutes of Health Criteria† 1990 (both are required for diagnosis)	Rotterdam Consensus Criteria‡ 2003 (two out of three are required for diagnosis)	Androgen Excess Society§ 2006 (hyperandrogenism plus one out of remaining two are required for diagnosis)
Hyperandrogenism‖	R	NR	R
Oligoamenorhhea or amenorrhea	R	NR	NR
Polycystic ovaries by ultrasound diagnosis		NR	NR

Abbreviations: R, required for diagnosis; NR, possible diagnostic criteria but not required to be present

*All criteria recommend excluding other possible etiologies of these signs and symptoms and more than one of the factors present to make a diagnosis.

†Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston (MA): Blackwell Scientific Publications; 1992.

‡Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fertil Steril 2004;81:19–25.

§Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. Androgen Excess Society. J Clin Endocrinol Metab 2006;91:4237–45.

‖Hyperandrogenism may be either the presence of hirsutism or biochemical hyperandrogenemia.

Polycystic Ovary Syndrome (PCOS)

EVALUATION

Differential Diagnosis

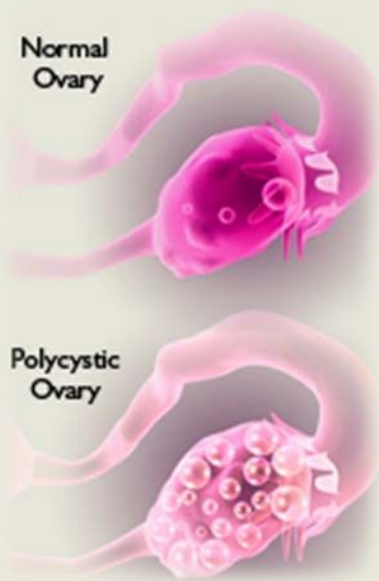
- Hypothalamic amenorrhea
- Premature ovarian failure
- Idiopathic hirsutism
- Other endocrinopathies: thyroid disorder, hyperprolactinemia, NC-CAH, Cushing syndrome, etc.
- Severe IR Syndromes (i.e., Syndrome X/Metabolic Syndrome)
- Neoplasm: rapid onset symptoms?
  - Ovarian (sertoli-leydig, granulosa-theca, hilus-cell)
  - Adrenal
  - Pituitary/hypothalamic
- Drugs (i.e., steroids)
- HAIR-AN syndrome
  - HyperAndrogenism,
  - Insulin Resistance,
  - Acanthosis

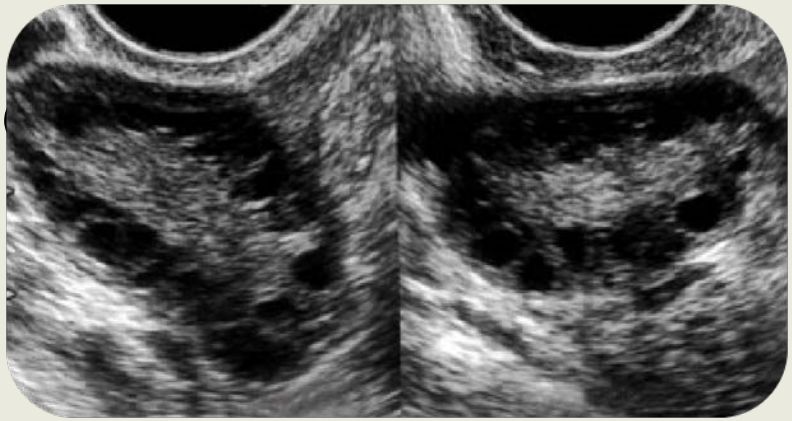
PCOS: Menstrual Dysfunction

- 25-30% of women with oligo-anovulation have PCOS
  - ≥35 day intervals or <10 bleeds per year
- 2/3 of patients with PCOS have oligo-anovulation
- PCOS patients may describe “normal” menses, but further investigation reveals chronic anovulation in ~25%
- Consequences:
  - Menstrual Dysfunction
  - Infertility
  - Endometrial hyperplasia/cancer

Polycystic ovaries ≠ PCO syndrome

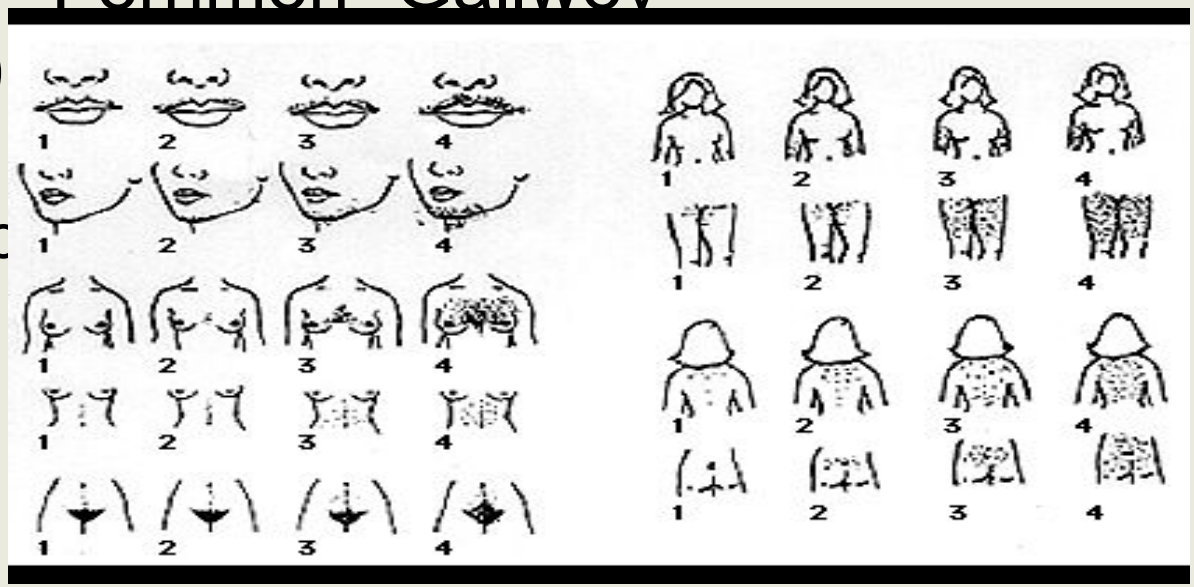
- Transvaginal sono is best
- Incidence decreases with age
- Sonogram Morphology:
  - >12 follicles/ovary @ 2–9 mm diameter
  - Volume: >10mL
  - +/- "string of pearls"
- Rule of 20%:
  - 20% of women with PCO have PCOS
  - PCO absent in ~20% with PC
  - Present ~20% without PCOS
    - Hypothalamic amenorrhea
    - Adolescents
    - Hyperprolactinemia





Assessing Hirsutism

- Hirsutism vs virilization: rapidly developing virilization or certain virilizing symptoms (i.e., clitoromegaly, voice deepening) warrants further evaluation
  - Modified Ferriman-Gallwey
    - 9
    - Sc



PCOS: Physical Exam

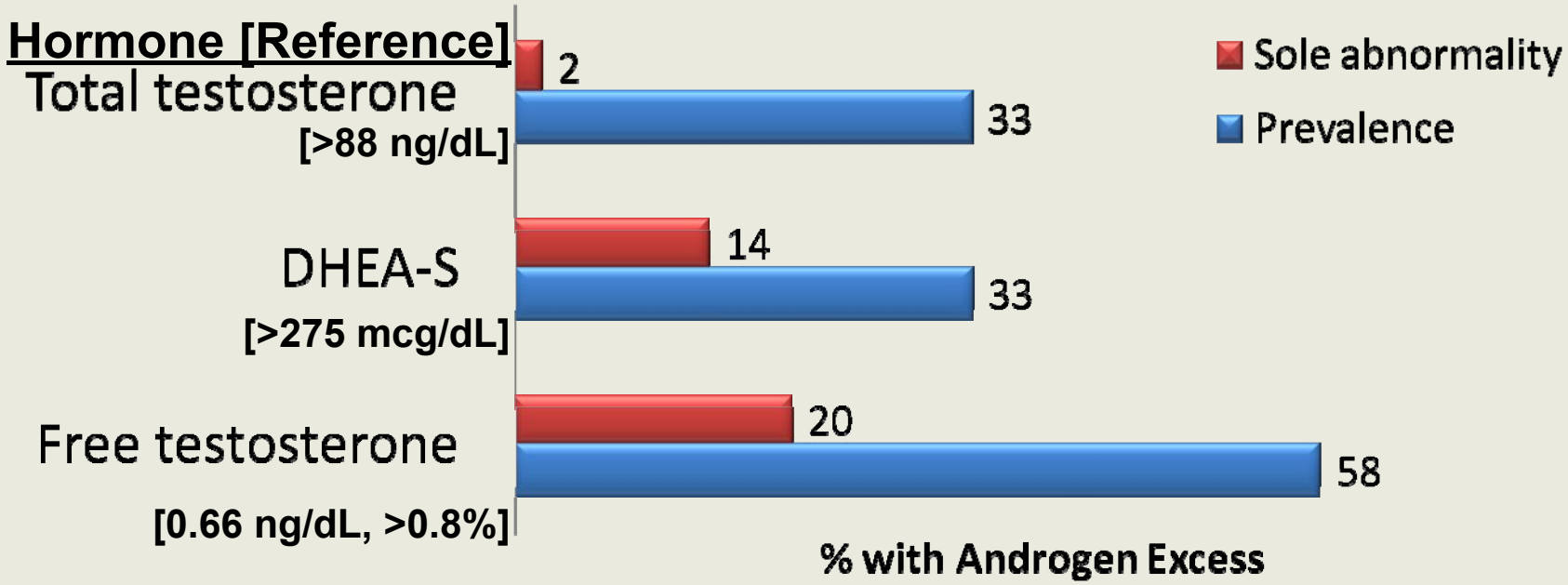
- Blood pressure
- Body mass index (kg/m^2)
  - >25 overweight
  - >30 obese
- Waist circumference > 35 inches, abnormal
- Acanthosis nigricans: insulin resistant
- Acne/alopecia: androgen excess
- Galactorrhea: hyperprolactinemia
- Thyroid
- Stigmata of Cushings? (striae, moon facies, etc…)

PCOS: Basic Work-up

- FSH & estradiol (E2) +/- LH:
  - premature ovarian failure (low E2; high FSH)
  - hypothalamic amenorrhea (low/normal E2; low FSH)
  - In [lean] PCOS, LH/FSH > 2
- Free testosterone, normally <0.8% free
- Prolactin & TSH
  - Mild elevations of prolactin more common in PCOS
  - Hypothyroidsim € hyperprolactinemia
  - NOTE: both conditions can produce PCO morphology on sonogram
- Progesterone in luteal phase to confirm ovulation
  - >3 ng/mL
  - Can corroborate with sonogram monitoring of follicular development

Hyperandrogenemia in PCOS

- A. Huang, et al., F&S, April 2010, N= 720 (NIH criteria)
- Hyperandrogenemia present 75%



PCOS: Evaluation

- DHEA-S
  - Mildly elevated in 30-40% PCOS
  - adrenal tumors >700 mcg/dL € Pelvic/Adrenal contrast CT
  - Dexamethasone suppression test

- 17-hydroxyprogesterone (17-OHP):
  - Ashkenazi Jews, Latina, Mediterraneans, Inuits, Yugoslavians
  - Nonclassical CAH: AR, ~5% of presumed PCOS
  - Measure a.m. during follicular phase
  - Nonclassical CAH >4 ng/mL
  - Borderline: 2-4 ng/mL € Cortrosyn stimulation test

PCOS: Optional Evaluation

- Total testosterone
  - Ovarian tumors >200ng/dL € get imaging
  - PCOS: upper limit of normal female, <80ng/dL
  - Use to calculate free testosterone
- 24-hr urinary cortisol
  - Screen Cushing's syndrome >50mcg/24h € need further testing

PCOS: Obesity

- NOT part of diagnostic criteria
- Common in PCOS, affects between 50 to 80%
- Waist-to-hip ratio >0.85 predicts insulin resistance better than BMI
- Worsens phenotype

PCOS: Overweight?

- Screen impaired glucose tolerance or Diabetes
  - oral GTT: Fasting glucose € drink 75 gram glucola € repeat 2-hour glucose; can also test insulin
    - Fasting: <100 normal; 100-125 impaired; >126 DM-II
    - 2-hour: <140 normal; 140-199 impaired; >200 DM-II
  - Fasting glucose/insulin < 4.5 (+/-)
- 20% annual risk of developing glucose intolerance

Metabolic Syndrome

- 15% of U.S. population
- 33% of PCOS!!
- Adult Treatment Panel III (others exist):
  - Elevated blood pressure ≥ 130/85
  - Increased waist circumference ≥ 35 in
  - Elevated fasting glucose ≥ 100 mg/dL
  - Reduced high-density lipoprotein cholesterol (HDL) ≤50 mg/dL
  - Elevated triglycerides ≥ 150 mg/dL

Polycystic Ovary Syndrome (PCOS)

TREATMENT: GOAL SPECIFIC

PCOS: Goal Specific Therapy

- Screen and manage comorbidities
- Hirsutism/acne/hair loss
- Protect/monitor endometrium
  - Ultrasound +/- endometrial sampling
  - HRT/OCP (+/- insulin sensitizing agents) for endometrial protection and menstrual regulation
    - Incidentally may reduce hyperandrogenism (hirsutism, acne, etc.)
- Fertility

PCOS: Co-morbidities!

- Insulin resistance, ~30%
- Type-II DM, ~10% (3-5x)
- Gestational diabetes (2.5x)
- Endometrial hyperplasia/ atypia/cancer
- Metabolic syndrome/syndrome X
- Sleep apnea/disordered breathing (Ehrmann, 2006)
  - related to IR NOT weight/BMI or androgens (30-40x)
- Depression
- Sexual dysfunction

PCOS: Probable Links

- Coronary artery disease
- Dyslipidemia
- Hypertension
- Ovarian cancer (?)
- Miscarriage (?)
- Pregnancy induced hypertension/PIH (?)

Prevention of CVD and DM

- Lifestyle: weightloss and exercise!!
- Metformin 1500-2000 mg daily if documented impaired glucose tolerance or metabolic syndrome, otherwise limited evidence for use.
- Statins: beneficial in long-term for prevention, but must avoid pregnancy, since category X

PCOS: Endometrial CA

- 56 obese PCOS women (Cheung,2001)
  - 36% hyperplasia € 2% cancer without tx
  - 9% atypia € 23% cancer without tx

- Women >50 yrs with endometrial cancer, PCOS present in 62.5%

Summary: Sequelae of biochemical aberrations

Biochemical abnormality	**Signs / Symptoms**	**Consequences**
High androgens & Low SHBG	Hirsutism; acne; Alopecia	Anovulation; Infertility
Chronic estrogen excess	Irregular menstrual cycles, menorrhaghia, dysfunctional menstrual bleeding	Endometrial hyperplasia/cancer; Ovarian cancer (?); Breast cancer (?)
Impaired glucose tolerance/Insulin resistance/ diabetes	Acanthosis nigricans Obesity/central adiposity	Diabetes; Gestational diabetes; Hypertension; PIH/preeclampsia (?)
Dyslipidemia	Abnormal lipid panel	CAD

Treatment of Hirsutism

Multi-step approach is most-effective:

- Hair removal: wax, laser, eflornithine, etc.
- OCPs for at least 3 months, (>18 months is best)
- Metformin (+/-)
- Continuous progestin therapy
- GnRH agonist (lupron): <6m use; many side-effects
- Anti-androgens (<u>USE with contraceptive</u>!):
  - <u>Spironolactone</u> (100-200mg/d): binds DHT intracellular receptor; in-utero risk: incomplete virilization of male fetus
  - <u>Finasteride</u> (2.5mg q 3 d to 5mg/d): inhibits 5-alpha- reductase (blocks T € DHT); in-utero risk: male fetus hypospadias
- Steroids: many SE, reduces androgens, ok short-term

Treating PCOS anovulatory infertility

Intervention	Cost	Risk of multiples
Lifestyle/ weight-loss	Low	No increase
Clomid/ Femara	Low	Modest increase (<10%)
FSH injections	High	Marked increase (20-30%)
Ovarian surgery	High	No increase, but limited efficacy
In vitro fertilization	High	Marked increase, but modifiable by limiting the number of embryos transferred.

Modified from Barbieri, Up-To-Date

PCOS: Weight Loss

- Frequency of obesity in women with anovulation and PCO: 30%-75% -- most before puberty

- 5-10% weight loss restores ovulation >55% < 6months (Kiddy, 1992)

- Weight-loss program for anovulatory obese women:
  - Lost 6.3 kg (13.9 lbs) on average
  - Decreased fasting insulin and testosterone levels
  - Increased SHBG concentrations
  - **92% resumed ovulation (12/13)**
  - **85% became pregnant (11/13)**

PCOS and Infertility: Metformin?

- Metformin (biguanide): improves insulin resistance
  - reduce hepatic glucose production & intestinal absorption
  - Increase peripheral glucose uptake
  - increase SHBG € reduce androgen levels
- Major side effect of metformin is GI (n/v/d)
  - Metformin 500mg qD for 1 week € 2000mg daily
  - Can use extend release dosing, qd @ dinner
- Risks/Contraindications
  - Renally excreted (Cr<1.4)
  - Hepatotoxic -- avoid with elevated transaminase
  - Lactic acidosis (RARE!)
  - Stop 1 day before IV contrast dye study or surgery

PCOS and Infertility: Metformin?

- MC-RCT, 6 months
- No screening for IR
- Medications started concomitantly
- No difference in SAB rates

N=626	CC + Plac N=209	Met + Plac N=208	CC + Met N=209
LBR, %	22.5	7.2	26.8
Preg/ovul, %	39.5	21.7	46
MGR, %	6	0	3

Legro et al., NEJM 2007

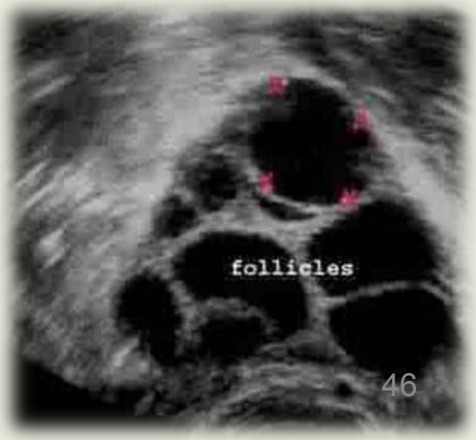
PCOS Fertility Options: Ovulation Induction (OI)/Superovulation (SO)

- Clomiphene Citrate: non-steroidal weak estrogen related to diethystilbestrol, SERM

- Clomid:
  - start cycle-day 2, 3, 4, or 5
  - take for 5 days (less common protocols exist)
  - Dose 50mg/day to 200 mg/day (take pills once per day, not bid/tid/etc…
- Ovulate ~80% € 60% pregnant < 6m for OI patients
- Consider letrozole/femara: aromatase inhibitor, may have less negative impact on endometrial thickness

PCOS Fertility Options: OI/SO (2)

- Gonadotropins: HMG, FSH
  - 60% live-birth 12-18 mo
  - Need careful monitoring (follicle scans, estradiol levels)
    - OHSS (~1-2%)
    - Multiple gestation risk (~20-30%)
    - Risk of multiples may be hard to modify
  - Combine with clomid to reduce risks and costs of treatment (i.e., start with clomid cycle day 3-7, then add gonadotropins)



PCOS Fertility Options: ART

- Assisted Reproductive Technologies (ie, IVF/ICSI)

  PROS

  – Highly successful in PCOS: >60% OPR/cycle in <35 yo
  – Efficient: Usually have supernumery embryos that can be cryopreserved for future use (~70%)
  – Can modify risk of multiples (i.e., elective single embryo transfer)

  CONS

  – [Relatively] expensive (per cycle) € though increasing evidence that this is more cost-effective per live born

PCOS Fertility Options: Surgery

- Laparoscopic wedge resection or ovarian drilling

  PROS

  – May avoid fertility treatment risks (i.e., multiples, OHSS)
  – May identify and treat other comorbidities (i.e., endometriosis, pain, adhesions)
  – Intraoperative findings may alter treatment decisions

  CONS

  – Relatively invasive
  – Doesn't universally restore ovulation ~50:50
  – Postoperative adhesions
  – Iatrogenic compromise to ovarian function/reserve
  – Limited data support its efficacy

PCOS: Pharmacotherapy summary

Therapeutic Category	Product Name	Dose	Use
Oral contraceptives	Various drugs containing estrogen and progestin component (avoid products containing levonorgestrel or norgestrel)	1 tablet daily PO for 21 days	Hirsutism, acne, hyperandrogenism
Antiandrogens	Spironolactone (Aldactone)	50 to 200 mg PO daily	Hirsutism
Antidiabetic agent	Metformin (Glucophage)	500 mg PO bid to 850 mg PO tid	Treatment of hyperinsulinemia, hyperandrogenism, ovulation
Estrogen agonist-antagonist	Clomiphene (Clomid)	50 to 100 mg PO daily, cycle days 5 to 9	Ovulation induction
Gonadotropins (used sequentially with hCG)	Menotropins (Pergonal; Humegon; Repronex)	Initial dose: 75 IU FSH/LH per day for nine to 12 days SC	Ovulation induction
	Follitropin-α (Gonal-F)	Initial dose: 75 IU FSH per day for five to seven days SC	
	Follitropin-β (Follistim)	Initial dose: 75 IU FSH per day for up to 14 days SC	

PCOS: Conclusions (1)

- Multifaceted condition with varying presentation
- No clearly accepted basis for diagnosis
- Significantly associated health consequences
  - Genetic and pre-natal implications
  - Metabolic disorder with risk of long term health complications: DM, cardiovascular, obesity, etc.
  - Reproductive repercussions: Endometrial hyperplasia € cancer; menstrual irregularities; infertility

PCOS: Conclusions (2)

- Treatment goals
  - Educate
  - Identify and monitor co-morbidities
    - i.e., hyperlipidemia, diabetes, endometrial hyperplasia
  - Modify associated long term health risks
    - i.e., diet, exercise, induce cyclic bleeding, medications
  - Treat patient concerns: effective therapies exist!
    - i.e., Hirsutism; infertility; cycle regulation