The Nuts and Bolts of Polycystic Ovary Syndrome

Kara S Hughan M.D.

Assistant Professor of Pediatrics
Division of Pediatric Endocrinology
Children's Hospital of Pittsburgh of UPMC
University of Pittsburgh School of Medicine

October 20, 2017

Learning Objectives

- Identify the diagnostic criteria for PCOS
- Identify risk factors that place PCOS women at high risk for cardiometabolic disturbances
- Select the best diagnostic test to document anovulatory bleeding in females with clinical findings suggestive of PCOS
- Highlight the key investigations of both reproductive & cardiometabolic features of PCOS
- Discuss management of menstrual, cutaneous & metabolic abnormalities in PCOS

Background

- Polycystic ovary syndrome (PCOS) is the **most common** endocrine disorder among women of reproductive age, affecting approximately **6% - 15%** of adult women[1,2]

[1]Knochenhauer et al JCEM 1998

[2]Azziz et al JCEM 2004

[3]Dumesic DA et al. Endocr Rev 2015

PCOS Background

- Characterized clinically by **oligomenorrhea** and **hyperandrogenism**

- **Three** different **diagnostic criteria** for PCOS, which presents up to 10 possible PCOS phenotypes:

NIH consensus criteria ,1990 (all required)	Rotterdam criteria, 2003 (two out of three required)*	AES definition, 2008 (all required)
Clinical and/or biochemical signs of hyperandrogenism	Clinical **and/or** biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Menstrual irregularity due to oligo- or anovulation	Oligo- **or** anovulation	Ovarian dysfunction – oligo-anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

* Rotterdam criteria based upon a 2003 concensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine consensus workshop group).

Background

- PCOS is associated with obesity (30-75%), problems with glucose regulation, dyslipidemia, hypertension, sleep apnea and cardiac dysfunction
- Hyperinsulinemia/insulin resistance with or without obesity is an integral component of PCOS with heightened risk of type 2 diabetes
- Controversy continues whether or not cardiovascular disease (CVD) is increased in PCOS

Origins of PCOS
The "Two Hit" Hypothesis

- Genetic or epigenetic factors reset reproductive and metabolic trajectories in early life, while

- Factors later in life influence the severity of the adult PCOS phenotype
  - Nutrition
  - Ethnicity/race
  - Other environmental influences

[1]Dumesic et al Rev Endocr Metab Disord 2007

The First Hit
Genetic or Epigenetic Factors

- Heritability
  - Twin studies show a strong genetic contribution to PCOS[1]
  - Several genes implicated with PCOS, each contributing a moderate effect[2,3]
  - Increased prevalence of PCOS in mothers (8-24%) and sisters (16-32%) of PCOS probands[4-6]

[1]Vink et al. J Clin Endocrinol Metab 2006, [2]Ewens et al JCEM 2010, [3]Goodarzi Nat Rev Endocrinol 2011, [4]Kahsar-Miller 2001, [5]Yildiz 2003, [6]Legro 1998

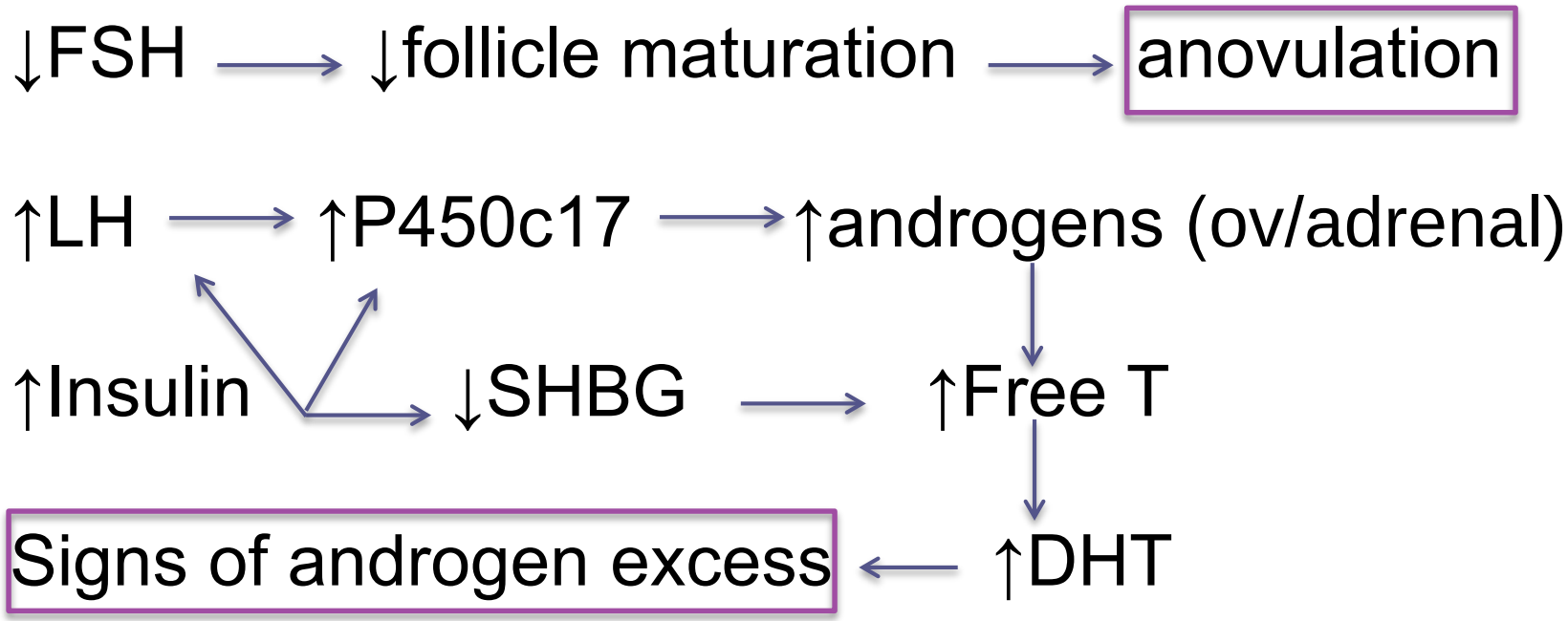
The Second Hit
Ethnicity/Race

	Prevalence (%)
Spain	6.5%
Southeastern U.S. Black White	6.5% 8.0% 4.0%
Greece	6.8%
United Kingdom	8%
Australia	8.7%

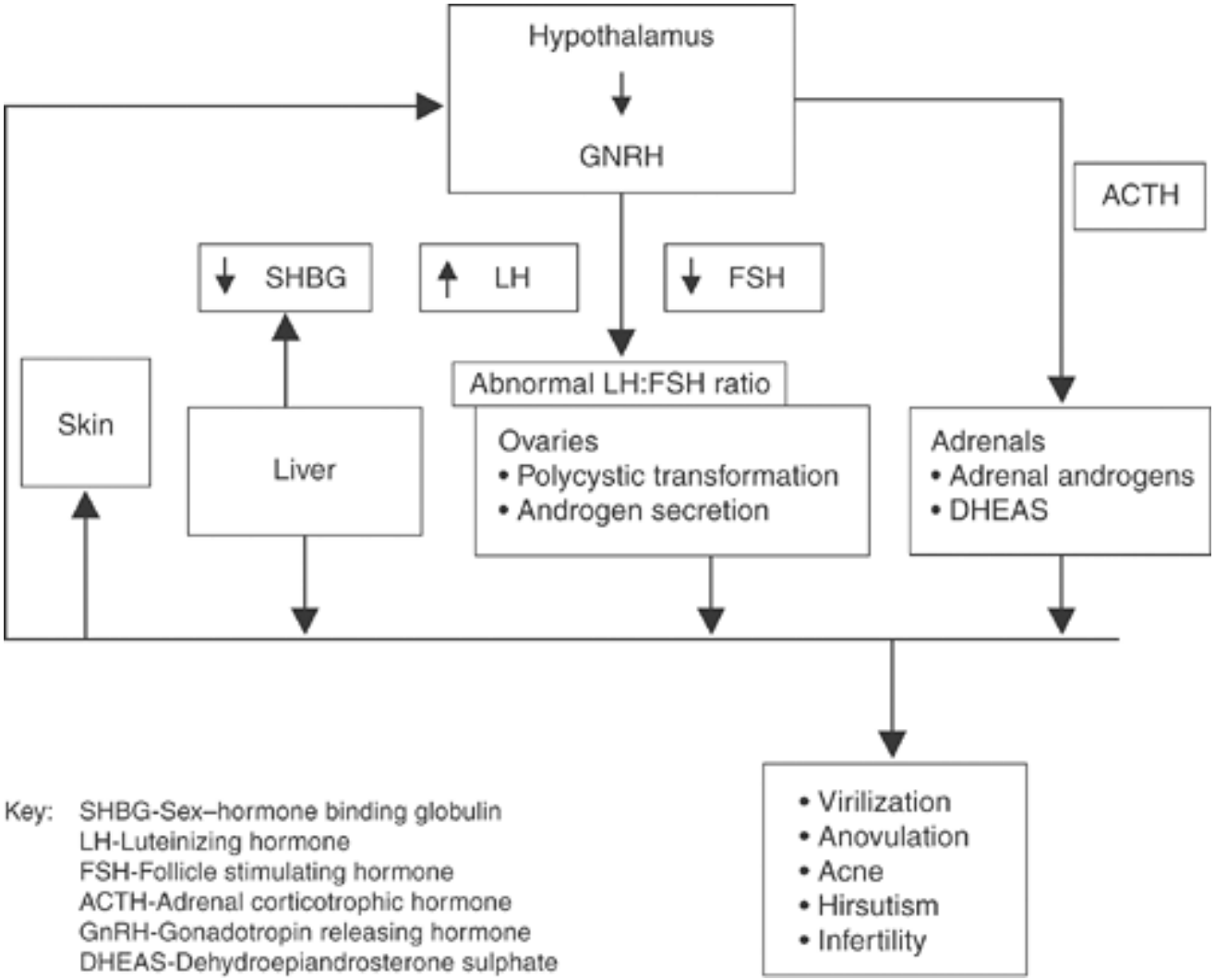
South Asians and Caribbean-Hispanic women with PCOS are more insulin resistant than affected women in other ethnic groups

Impact of Lifestyle

- **Obesity** influences PCOS phenotype by unmasking or amplifying symptoms of **hyperinsulinemia** and **hyperandrogenism**



PCOS Pathogenesis



Key: SHBG-Sex–hormone binding globulin
LH-Luteinizing hormone
FSH-Follicle stimulating hormone
ACTH-Adrenal corticotrophic hormone
GnRH-Gonadotropin releasing hormone
DHEAS-Dehydroepiandrosterone sulphate

Environmental

- Bisphenol A
  - Widely used estrogenic industrial plasticizer
  - Excreted in urine & detectable in 92% of American's urine specimens
  - Elevated in PCOS women
  - Displaces androgen from testosterone's binding protein (SHBG) to increase androgen availability
  - Enhances ovarian androgen production

PCOS Characteristics

- **Endocrine Disturbances**
  - Oligo- or amenorrhea / oligo- or anovulation
  - Hyperandrogenism
    - Hirsutism
    - Acne
    - Alopecia
  - PCO morphology
  - ↓ fertility
- **Metabolic Disturbances**
  - Obesity
  - Insulin resistance
    - Impaired glucose tolerance (IGT)
    - Type 2 diabetes mellitus
  - Dyslipidemia
  - Hypertension
  - Obstructive sleep apnea
  - ?CVD

Endocrine Disturbances

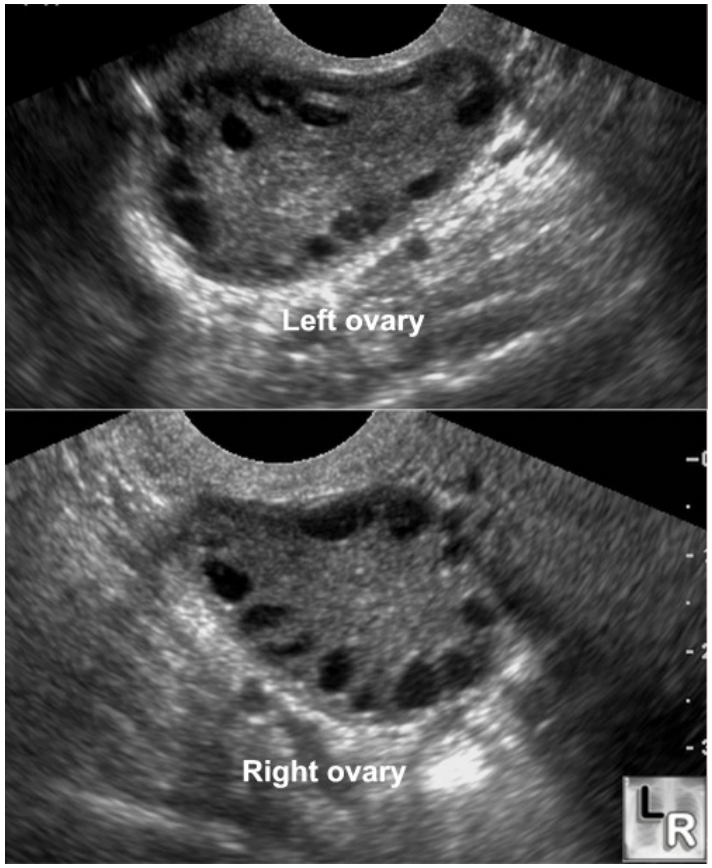
- Oligo- or amenorrhea
  - Menstrual cycle frequency < 8 cycles/year
- Hyperandrogenism
  - Hirsutism in a male pattern
  - Acne
  - Alopecia in a male pattern

PCO Morphology

- Presence of >10-12 follicles/cysts and 2-8 mm in diameter that are peripherally arranged in a “string of pearls” appearance

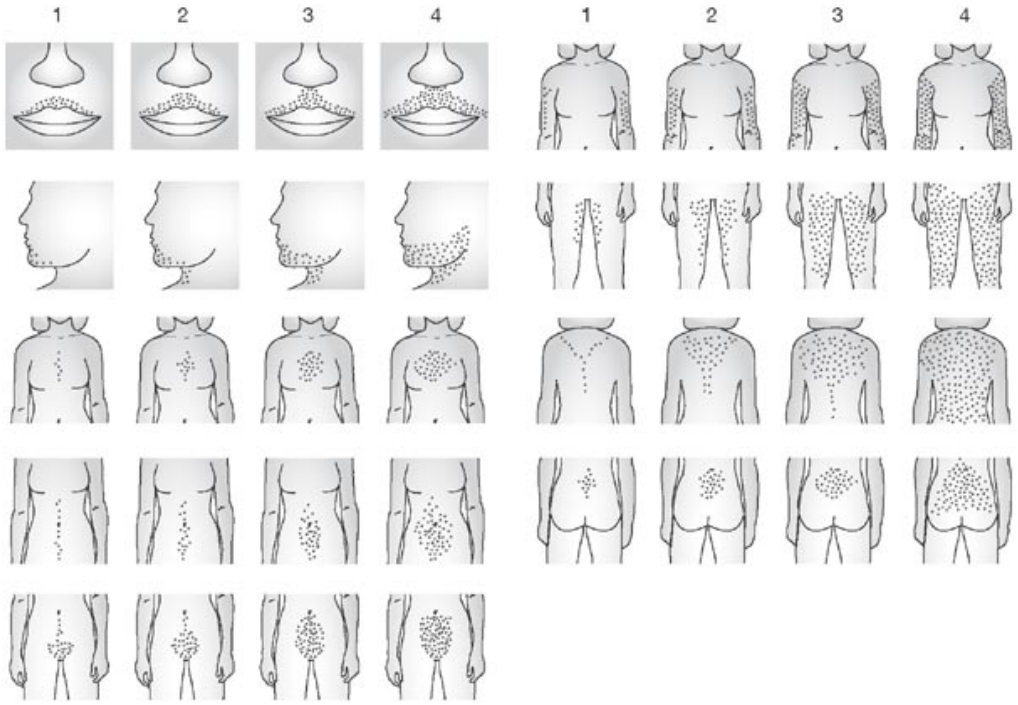
and/or

- Increased ovarian volume (>10mL or cm^3)
- Does not apply to females taking OCPs



Ferriman-Gallwey Scoring of Hirsutism

- Hirsutism = excessive growth of facial or body hair, specifically terminal hair (long, coarse and pigmented), in an androgen-dependent /male pattern in women



- F-G score ≥ 6-8 defines hirsutism

Yildiz Nat Clin Prac Endo & Metab 2008

Differential and Work-up for PCOS

✓ TSH
✓ Prolactin (PRL)

Evaluate for Hypothyroidism (↑TSH) and Hyperprolactinemia

✓Total and free Testosterone (T) and DHEA-S

Evaluate for PCOS

· ↑ Total/free T and DHEA-S or
· Hirsutism and/or significant acne and
· Normal TSH, PRL, 17-OHP
· Consider pelvic ultrasound if labs are normal and there is a history of primary amenorrhea

History of primary amenorrhea without significant clinical hyperandrogenemia?

✓ LH and FSH; if normal & prior labs are normal, consider pelvic ultrasound

Evaluate for gonadal failure (↑LH and FSH)

Define internal anatomy or structural abnormality :
· Ovarian size (>10cm^3 c/w PCO)
· Uterine length (>3.5-7 cm is pubertal, 7-8 cm is adult)
· Presence of peripheral cysts/multiple follicles
· Endometrial stripe thickness

Work-up of PCOS

Clinical signs of virilization?

✓ Total/free T and DHEA-S

Evaluate for virilizing tumor

· If above hormones are ~2x normal, consider CT/MRI of adrenals +/- pelvic US

Clinical signs of Cushing's syndrome?

✓ 24-hour urine for free cortisol (UFC) and correct for patient's BSA

Evaluate for Cushing's syndrome

· If UFC is elevated, refer to Endo for dexamethasone depression test

History of irregular menses and early pubic hair development?

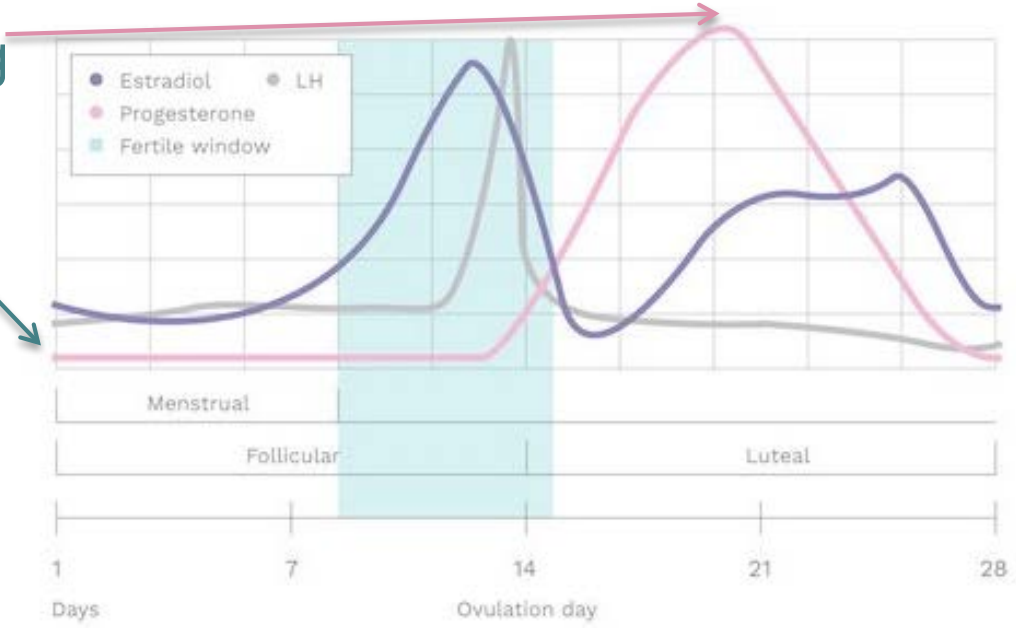
✓17-OH Progesterone (17-OHP)

Evaluate for Non-Classical CAH (NC-CAH)

· If 17-OHP elevated, refer to Endo for ACTH stimulation test

Steps in PCOS Work-up

- Evaluate for clinical/hormonal criteria for PCOS
- R/o other causes of hyperandrogenism & oligomenorrhea
- Next, consider documenting anovulatory bleeding (if oligomenorrhea)
  - Measure fasting morning progesterone level 3 weeks after her LMP
  - If low (<10 ng/mL), ovulation has not likely occurred



Association With Metabolic Syndrome (MetS)

- Various definitions or criteria exist but generally include:
  - Increased waist circumference
  - Elevated glucose (fasting or post-prandial)
  - Elevated triglycerides and/or low HDL
  - Elevated blood pressure
- MetS is 2.5-4x more common in women with PCOS than in general population[1]
- The odds of adolescent girls with PCOS having MetS is 4.5-6x higher than that of girls in the normal population[1] (after adjusting for BMI)

[1]Behboudi-Gandevani S et al Clin Endocrinol 2017

Metabolic and CV Disease Risk

- High risk in all PCOS patients with:
  - MetS
  - Type 2 diabetes mellitus
  - Known CV or kidney disease
- At risk in PCOS patients with:
  - Obesity
  - Smoking
  - Dyslipidemia
  - HTN
  - Impaired glucose tolerance

Key Risk Factors to Assess

- BMI
- Blood pressure
- Baseline fasting lipid profile, especially if +FHx of hyperlipidemia
- If BMI >27 kg/m^2, 75 g oral glucose tolerance test (OGTT)
- Mood disturbances: depression, abnormal eating patterns and reduced QOL

Long-Term Treatment Goals For Patients With PCOS

- **Suppress androgen production and action**
- **Regular menstrual shedding of the endometrium** in women not desiring pregnancy, to decrease the risk of developing endometrial hyperplasia
- **Promote fertility/ovulation** in those desiring pregnancy

Long-Term Treatment of PCOS Patients With Metabolic Syndrome

- **Lifestyle modification** (diet + exercise +/- behavioral therapy) is the first-line therapy
- 3-6 months in a formal exercise program resulted in:
  - Reductions in BMI, waist circumference, BP[1], HDL and TGs[2,4]
  - Increased insulin sensitivity[3,4]
  - Improved menses, ovulation, pregnancy rate[5]
  - Improved VO_{2max}[2] and aerobic fitness[3]

[1]Vigorito JCEM 2007, [2]Brown A et al Medicine & Sport Science in Sports & Exercise 2009, [3]Redman et al Fertility and Sterililty 2011, [4]Hutchinson S et JCEM 2011, [5]Palombo S et al. Hum Reprod 2008

Long-Term Treatment of Patients With PCOS and Metabolic Syndrome

- Add-on medication often includes **metformin** if there is mild/moderate obesity with:
  - impaired fasting glucose or impaired glucose tolerance
  - signs of insulin resistance such as skin tags or acanthosis nigricans
  - marked hyperlipidemia
  - contraindication to OCP use

Metformin

- Improves the effectiveness of insulin produced by the body
- Beneficial **for metabolic/glycemic abnormalities** and **for improving menstrual irregularities**
- SEs: nausea, abdominal pain, diarrhea; lactic acidosis (rare)
- It has limited benefit in treating hirsutism, acne, or infertility

Exercise + Diet + Metformin

48 week intervention→ Ovulation and androgen concentrations

A) Metformin 850 mg BID
B) Lifestyle modification + Metformin
C) Lifestyle modification + placebo
D) Placebo only

Results

-↓ circulating androgens only in the combo (B) group

-No difference in ovulation rates among groups but was strongly associated with weight loss

Hoeger K et al Fertility and Sterility 2004

Exercise + Diet + Metformin

6 months of 150 min/wk exercise combined with low-calorie diet plus:

A) Metformin 500-2000 mg per day

B) Placebo only

Results

-↓ circulating testosterone at 4 months with no group differences

-No difference in ovulation rates

-Weight decreased at all points in both groups, no group differences

-Metformin + lifestyle added little reproductive or glycemic benefit

Ladson G et al Fertility and Sterility 2011

Long-Term Treatment of Patients With PCOS and Acne/Hirsutism

- **OCPs** are the 1st line tx of hirsutism & acne in women with PCOS, 6 month trial recommended
- Effect can be potentiated when combined with **spironolactone**, a peripheral androgen receptor blocker (50-100 mg BID)
  - SE: hyperkalemia, risk of feminizing a male fetus if used in pregnancy, menstrual dysfunction
  - Because of the latter two reasons, it is recommended that an OCP be used in combo

Alpañés M et al Eur J Endocrinol 2017

Actions of OCPs

Progestin

-Inhibits ovulation by **suppressing LH** from the pituitary

-Androgenic potential, especially 1st and 2nd generation progestins

-Creates thick cervical mucus that slows sperm transport

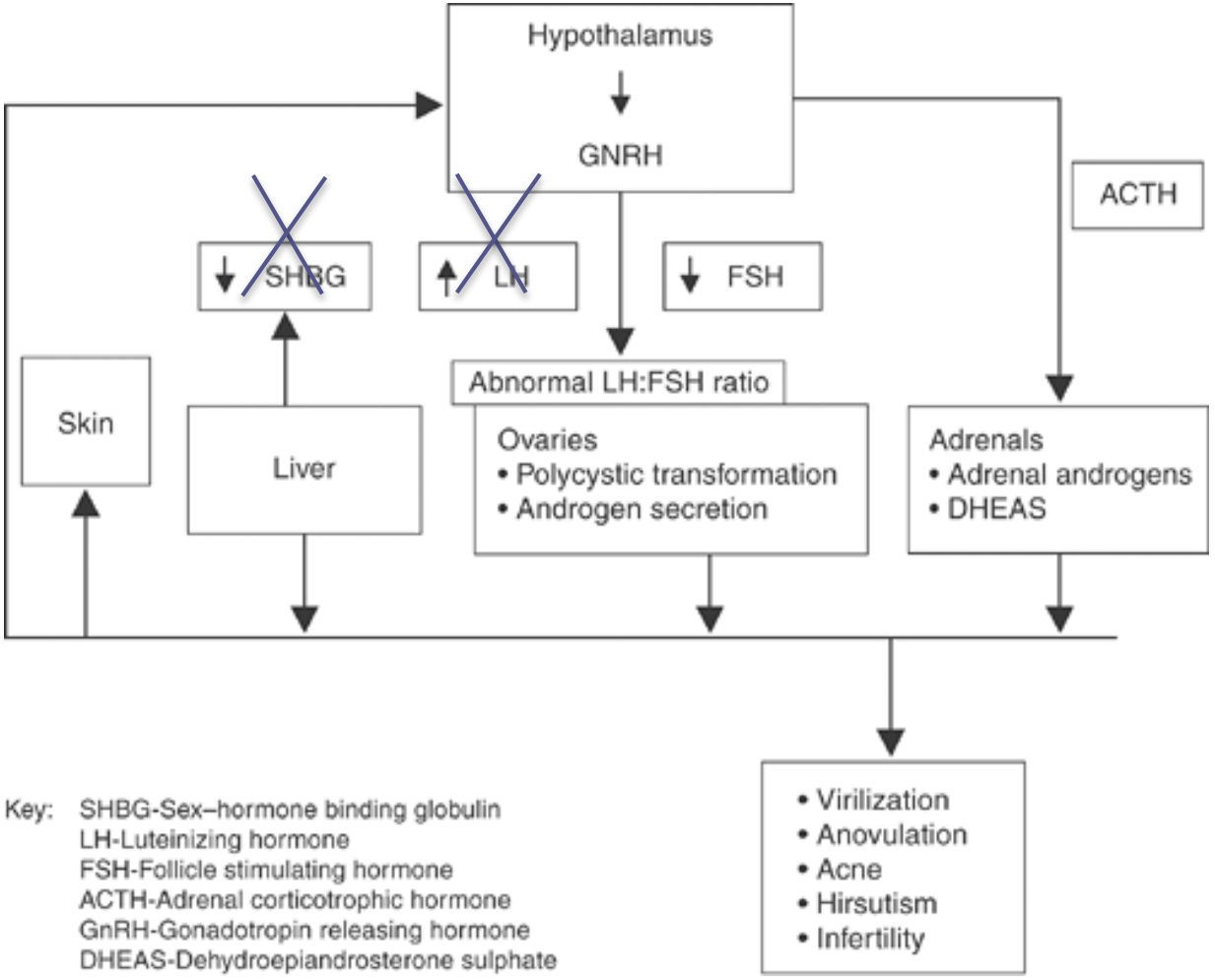
Estrogen

-Inhibits ovulation by suppressing FSH which inhibits follicle development and **suppresses LH surge**

-**Increases SHBG levels**

-Accelerates ovum transport which decreases fertilization time

Actions of OCPs in PCOS Treatment



Impact of OCPs

Side effects:

-Abnormal menstrual bleeding, nausea, breast tenderness, headache, mood changes

-No association with weight gain[1]

Absolute contraindications:

-Smoker > age 35

-HTN (SBP≥160 mmHg, DBP≥100 mmHg)

-History of or current VTE

-Migraine with focal neurological symptoms

-Known thrombogenic mutations (ex. Factor V Leiden, etc)

-History of stroke, ischemic heart disease, complicated valvular heart disease

[1]Gallo MF et al 2011 Cochrane Review

OCP Use and Related Health Concerns

- Glucose metabolism
  - Some studies indicate impairment of glucose tolerance during OCP use
  - Meta analysis revealed not enough data to make conclusions about risk[1]
- Lipid metabolism
  - Increase in HDL and triglycerides[1,3]
- Thromboembolism
  - No conclusive data in women with PCOS
  - General OCP users have 3-4x risk for VTE
  - Risk is estrogen dose-dependent and risk decreases after 1 yr of use[2]

[1]Halperin et al Human Reproduction (meta analysis) 2011, [2]Gillum et al JAMA 2000, [3]Alpañés M et al Eur J Endo 2017

Preferred OCPs for PCOS

- 3rd generation OCPs
  - Desogestrel: Kariva, Ortho-Cept/Desogen
  - Norgestimate: Ortho-Cyclen, Sprintec
- 4th generation OCPs
  - Drospirenone: Yaz (Gianvi, Loryna), Yasmin (Ocella, Syeda, Zarah), Beyaz and Safyral
  - Caution given two studies reporting 2-3x greater risk of VTE than levonorgestrel-containing pills (2nd generation)

Acne In PCOS

- In general, OCPs are shown to be effective treatment for acne
- Two studies compared **OCP vs. placebo** for 6 cycles[1,2]
  - Total, inflammatory and non-inflammatory lesions improved with OCP
- One study compared **OCP vs. metformin** x 12 months[3]
  - Both treatments were equally effective

[1]Maloyney et al 2008, [2]Koltun et al 2008, [3]Harborne et al JCEM 2003

Hirsutism In PCOS

- **Vaniqa 13.9% cream** (eflornithine)- inhibition of topical hair growth by inhibiting the enzyme needed for hair growth (treat BID x 8 weeks)
  - SEs: rash, stinging, redness, acne
- Temporary cosmetic strategies (bleaching, shaving, waxing, etc)
  - SEs: painful, erythema, scarring
- Mechanical methods of hair removal (laser, electrolysis)
  - SEs: expensive but efficient, scarring, dyspigmentation

Other Metabolic and Mood Co-Morbidities

- **Dyslipidemia**
- Glucose abnormalities
- Hypertension
- Mood disturbances including depression and anxiety

Dyslipidemia in Obesity & PCOS

- Combined dyslipidemia pattern:
  - Mild elevation in LDL
    - Increased intake of simple carbs drives hepatic production of VLDL, which can cause increased LDL in some
  - Moderate-severe elevation in TG
    - More FFAs delivered to liver from expanded adipose tissue
  - Low HDL
    - Reduced lipolysis
  - Mild elevation in Total Cholesterol

Dyslipidemia Risk factors

- +FHx
  - MI, angina, CABG or PCI, sudden cardiac death
  - Parent, grandparent, aunt, uncle
  - <55 yo for males, <65 yo for females
- HTN that requires drug therapy
- Smoking
- BMI ≥ 25 kg/m^2
- Presence of high-risk condition (such as T1DM/T2DM)

Statins

- HMG-CoA reductase inhibitors
  - Inhibits cholesterol synthesis in hepatic cells
- Lowers LDL, some decrease in TGs, modest increase in HDL
- FDA approved for ages 10-18
  - Postmenarcheal
  - Pravastatin approved ≥ age 8
- Magnitude of effect is specific to dose
- SEs: elevated liver enzymes, myopathy, rhabdomyolysis

Statins

- Short-term safety and efficacy data is positive
- Risk during pregnancy
  - Cholesterol is critical for embryonic cell signaling & production of steroid hormones
  - 2004 review of FDA reports of statin exposure during pregnancy
    - 214 pregnancies
    - 70 were evaluable
    - 31 had adverse outcomes
      - 22 structural defects – severe midline CNS, limb, VACTERL
      - 4 IUGR
      - 5 IUFD

Hypertriglyceridemia

- >500-1000 mg/dL = risk for pancreatitis
  - Limit dietary fats
  - Start fish oil, max 4g/day; fibrates or niacin are additional options with greater side effects

- 150-499 mg/dL
  - May be a role for fish oil here
  - Reduce simple sugar intake (sweetened beverages, cereals, baked goods)

Initial Treatment of Hypertriglyceridemia

- 25-30% calories from fat, ≤ 7% from saturated fat
- Cholesterol<200 mg/d
- **Decrease sugar intake**
  - Replace simple sugar with complex carbs
  - No sugar-sweetened beverages
- Increase dietary fish to **increase omega-3 fatty acids**; supplements:
  - 1000 mg of DHA and EPA
  - Side effects = indigestion, gas
  - Mechanism not well-understood

PCOS Management Goals

- Provide expectations of various therapies, risks/benefits and side effects
- Arrange follow-up visit in 4-6 months to review lifestyle and symptom progress, assess side effects and advise further management
- Set realistic goals to permit an individualized strategy

Dumesic Patient-Centered Management of Hirsutism 2011

Thank You!