PCOS: Background

- The intersection of sex hormones & metabolism
- Reproductive and endocrinologic/metabolic features
- Prevalence ~10%
- A multi-factorial, polygenic disorder with variable phenotypes
- PCOS is under-diagnosed and under-treated
  - Multiple cardiovascular risk factors
  - High conversion to diabetes

Polycystic Ovary Syndrome

- **2003 ESHRE/ASRM Consensus Conference Definition: 2 of 3 criteria**
  - Irregular menstrual intervals
  - Hyperandrogenemia
  - Polycystic ovaries *In absence of other etiologies
- **2011 AES criteria: presence of three features**
  - androgen excess (clinical and/or biochemical hyperandrogenism)
  - ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology)
  - exclusion of other androgen excess or ovulatory disorders

Polycystic Ovary Syndrome

- Endocrine Society 2013
  - Adult
    - ESHRE/ASRM criteria
  - Adolescent
    - presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea
  - Perimenopausal & menopausal women
    - well-documented long-term history of oligo/amenorrhea and hyperandrogenism during reproductive years

PCOS – Variable Presentations

- Earlier
  - Irregular menstrual intervals
  - Hirsutism
  - Acne
  - Alopecia
  - Weight gain
- May present in late teens or early 20's associated with a trigger:
  - Starting or stopping OCP
  - Gaining weight in college
  - Change in physical activity
  - Pregnancy

Later:

- Dyslipidemia
- IR/IGT/T2D
- Hypertension
- Fatty liver
- Obstructive sleep apnea
- Eating disorders
- Endometrial carcinoma
- DUB
- Miscarriages, preterm births, stillbirth, gestational diabetes

It's not just about obesity…..
…..compared to age- & weight-matched controls

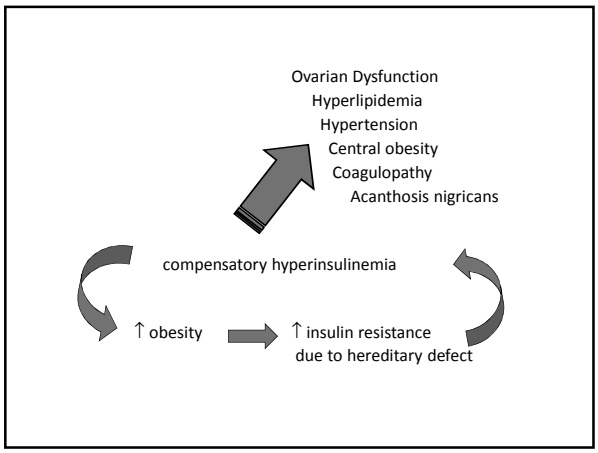
- PCOS women have higher ***prevalence*** of hyperinsulinemia
  - *Clin Endocrinol Metab* 1987;65:499–507
- PCOS women have a ***greater degree*** of hyperinsulinemia
  - *Diabetes* 1989;38:1165–1174
- 16% vs. 6% of PCOS develop diabetes at menopause
  - *Fertil Steril* 1992;57(3):505-13

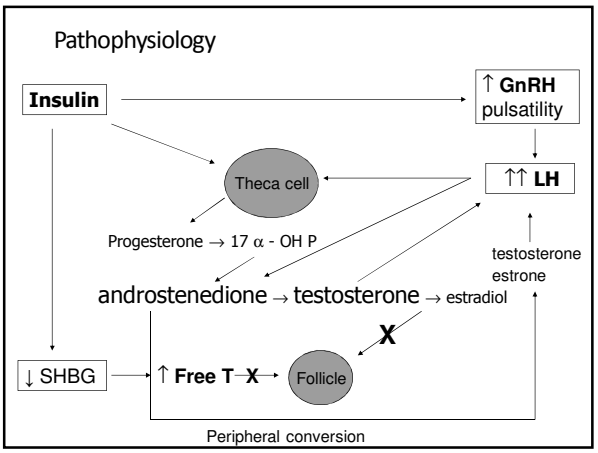
Obstetric Complications

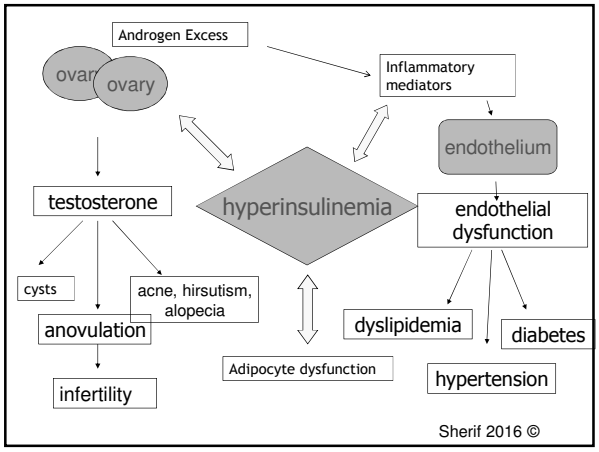
N = 4982 PCOS, N = 119,692 Controls

RISK	OR	95% CI
Gestational DM	3.43	2.49 – 4.74
PIH	3.43	2.49 – 4.74
Preeclampsia	2.17	1.91 – 2.46
Preterm birth	1.93	1.45 – 2.57
C-section	1.74	1.38 – 2.11
NICU admission	2.32	1.40 – 3.85

Qin JZ, Reprod Biol Endocrin 2013







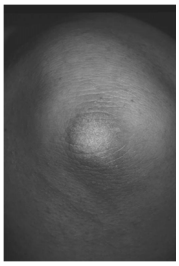
History

- Abnormal menses:
  - Oligomenorrhea or amenorrhea
  - Menorrhagia and metrorrhagia
- Reproductive abnormalities:
  - Infertility **
  - Multiple miscarriages
  - Preterm births and stillbirths
- Endocrine disturbances:
  - Rapid weight gain
  - Gestational diabetes
  - Diabetes
- Family history of premature cardiac disease
- Mothers or sisters with PCOS or infertility (24%)
  - Battaglia 2002 Human Repro
- Brothers with early balding (age<30) and other signs of excess androgens

Physical Examination

- Elevated blood pressure
- Signs of hyperandrogenism
  - Alopecia - depends on androgen receptors
  - Hirsutism - diffuse
  - Acne, often in an androgenic distribution
  - Seborrhea
- Signs of insulin resistance
  - Acanthosis nigricans – depends on pigmentation
  - Skin tags
- Central obesity (lean with abdominal fat)

Acanthosis nigricans



Initial blood tests for oligomenorrhea

#1 Urine Pregnancy Test
#2 TSH and free T4
#3 Prolactin

Blood Tests

- After excluding:
  - Pregnancy — Urine pregnancy test
  - Hypothyroidism — TSH
  - Pituitary Adenoma — Prolactin
- Measure:
  - Total testosterone & DHEAS (not DHEA)
  - LH & FSH
  - 17 α-OH progesterone
  - If suspicion of Cushing's disease: 24° urinary cortisol

Labs to support diagnosis

- Total testosterone > 50 ng/dL
  - Reference range: 14-76, Assays often unreliable

If testosterone >200, refer immediately

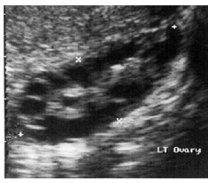
DHEAS 200-300 in PCOS

If DHEAS >600, refer immediately

- LH : FSH > 2 : 1
- 17-alpha-hydroxyprogesterone > 200, refer

Transvaginal sonography

- 10-12 peripheral cysts
- < 10mm diameter
- String of pearls



Frequently observed lab abnormalities

- High TSH with normal free T_4
- Elevated ALT & AST
- Elevated WBC's and CRP
- Dyslipidemia
  - High TG and low HDL

Summary of Diagnosis

1. History of irregular menstrual intervals
2. High androgens - either
   - Signs: severe cystic acne, alopecia and/or hirsutism OR
   - Labs: High serum testosterone and/or DHEAS
3. Polycystic ovaries on transvaginal ultrasound

Traditional Treatment

• Oral contraceptives	Oligomenorrhea Hirsutism Acne Alopecia
• Anti-androgens	Hirsutism Alopecia
• Clomiphene	Infertility

Oral contraceptives: benefits

- Increase SHBG & decrease free testosterone
- Improve hirsutism, alopecia & acne
- Decrease risk of endometrial cancer
- Regulate cycles

Sherif, Am J Ob/Gyn 180, 1999

Anti-androgens

- Spironolactone 100mg BID
  - 3-6 months to see improvement, especially in alopecia
  - Teratogen
- Alpha-reductase inhibitors: flutamide, finasteride
  - Transaminase elevations
  - Teratogen
- Ornithine decarboxylase inhibitors: eflornithine
  - 30% response rate at six months

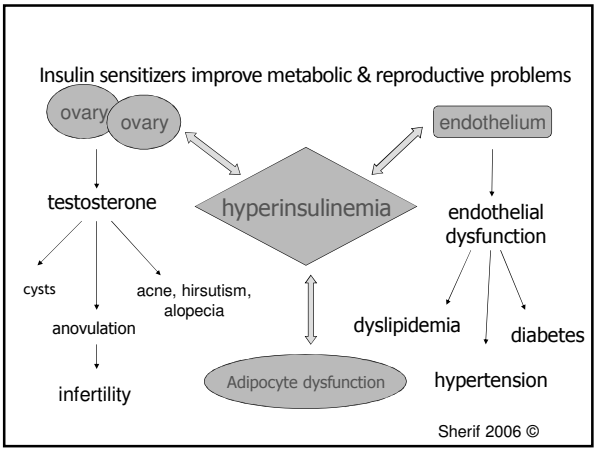
Treat *insulin resistance* to improve reproductive, androgenic and cardiometabolic problems

- Lifestyle
  - Nutrition
    - Decrease both calories & simple carbohydrates
  - Increase physical activity and muscle mass
  - Sleep 8 hours per night
- Insulin-sensitizing medication - the rationale for metformin
- Insulin-sensitizing supplements

The rationale for metformin

- Benefits:
  - Weight loss (minimal)
  - Improved lipid profile
  - Improved acne, hirsutism and alopecia
  - Normalization of transaminases
  - Ovulation & pregnancy
    - Cochrane meta-analysis: first-line agent for anovulation
- Side effects
  - Gastrointestinal: diarrhea, nausea
  - Decreased B-12 absorption and ↑ homocysteine

Lord, BMJ, 2003



Supplements with insulin-sensitizing properties

- D - chiro inositol & myo-inositol
- Vitamin D
- Cinnamon
- Chromium 250mg TID
- N-acetyl cysteine 500mg
- Alpha lipoic acid
- Resveratrol

Summary of Management

1. Nutrition counseling & increase physical activity
2. Metformin for metabolic abnormalities
3. Consider supplements
4. Hormonal contraception for dermatologic problems
5. Screen early for
   - Type 2 diabetes – A1c
   - Fatty Liver - transaminases
   - Hypothyroidism – TSH, free T4
   - Sleep apnea – STOP BANG
   - Depression, eating disorders

Cases

Case 1
16 year old girl diagnosed with PCOS

- History:
  - Mother brings her 16 year old daughter with PCOS because her symptoms are "out of control."
  - She takes OCP since age 15 and has monthly menstrual bleeding
  - Menarche age 11
  - Breast development started age 8, some pubic hair age 9
  - In spite of OCP, she has severe facial hirsutism. Shaves once or twice a day
  - She has noticed that she can see more of her scalp
  - She has cystic acne on her back and upper chest
  - She runs track in the spring and fall
  - She is greatly embarrassed by her hirsutism – also on thighs

Case 1
16 year old girl diagnosed with PCOS

- Vital signs: 90/60 5'1" 135# BMI 25.5
- Physical Examination:
  - Healthy-appearing
  - No acanthosis nigricans
  - Normal lungs, heart, abdomen
  - 9/10 hirsutism on face and neck and thighs
  - Moderate alopecia
  - Short fingers
  - Cystic acne scars on chest and upper back and upper arms
  - Normal external genitalia

Case 1
16 year old girl diagnosed with PCOS

- Labs
  - Normal CBC, chemistry, LFTs, TSH
  - Sex hormones not measured since she is on OCP
- One additional test: 21-hydroxylase enzyme
  - Positive for V281L mutation – homozygote
- Diagnosis: Non-classical Congenital Adrenal Hyperplasia

Case 1

Non-classical Congenital Adrenal Hyperplasia

- 21-hydroxylase mutation impairs the ability of the adrenal gland to produce cortisol. In response, it works harder. When it works harder, it produces more androgens.
- Presents after puberty but many patients have clues early on:
  - Early menarche
  - Early breast development
  - Rapid growth in elementary school initially, often the tallest
- More common in Greek, Italian, Jewish, Latina women, but still present in many ethnicities

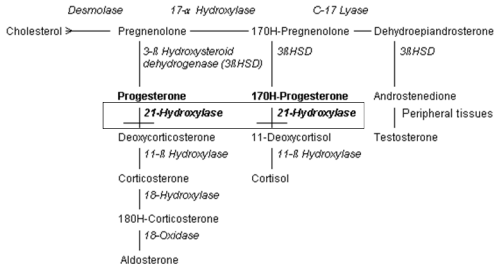
Case 1

Non-classical Congenital Adrenal Hyperplasia

21-hydroxylase mutation

- Later:
  - Relatively short after puberty; shorter than mother or sisters
  - Short fingers
  - Irregular menstrual intervals
  - Severe hirsutism, severe alopecia, severe acne – may be difficult to control
  - Metformin may not cause ovulation or improvement in hyperandrogenemic symptoms

Case 1



21-hydroxylase enzyme mutation in PCOS & CAH

GnRH increases adrenal androgen production: DHEA-S, A, T

Adapted from Deaton, AFP, 1999

Case 1

Non-classical Congenital Adrenal Hyperplasia Treatment

21-hydroxylase mutation

- Giving very low-dose steroids signals the adrenal gland to stop working so hard to make cortisol
- Indirectly, the adrenal gland makes less androgens
- Once the adrenal gland stops making excess androgens, it is easier to
  - Treat severe hirsutism or alopecia or cystic acne
  - Ovulate and conceive
- Metformin and spironolactone may still be helpful

Case 2

A 26 year old woman is in the office to establish care – new health insurance & has to choose a primary care physician

- **Her main concern: she would like a refill on birth control pills**
- She ran out of birth control pills six months ago and didn't renew because she didn't have insurance. Since then, she has had only two menstrual periods. She figured that it wasn't unusual because she has been on the pill for ten years so her body has to get used to being off the pill.
- When asked why she has been on the pill for so long, she said the doctor told her the pill would regulate her menstrual periods. She doesn't remember whether it was to "regulate" the very heavy bleeding, or "regulate" the severe menstrual cramps, or something else.
- When asked, she thinks her periods were "regular," meaning that they seemed to come every month – sometimes in the beginning of the month, sometimes in the middle of the month, or the end of the month. However, compared to her friends, it was not so predictable.

Case 2

A 26 year old woman

- Medical History: Nothing significant
- Surgical History: Wisdom teeth extraction
- Family History: Mother – diabetes
  Father – hypertension
  Sister – healthy, 1 child
  Maternal aunt – 1 child, miscarriages
- Medications: None
- Vitamins, minerals, supplements: None
- Drug sensitivities, allergies: None

Case 2

A 26 year old woman

- Review of systems
  - Had rapid weight gain. Gained 30# in college – but was able to lose the weight with low-carb eating and going to the gym a lot.
  - Another doctor told her that her "sugar was a little high" when she had a physical 2 years ago, and to repeat the blood test when she was fasting, but she didn't repeat it.
  - Her hair has always been "thin." It runs in the family. It seems to be getting thinner. She has no facial hair but had a lot of acne before she went on the pill at age 15.
- Sexual history:
  - She has been sexually active with men since age 19 and always used contraception until six months ago. She has never been pregnant. She has never had a STI. Since she has not had the birth control pill in the last six months, she and partner are using withdrawal method every time and it seems to be working!

Case 2

A 25 yo woman is here to establish care

- Vital signs: BP 130/88 HR 88 Ht 5'4" Wt 184# BMI 32
- Physical Exam findings:
  - Mild diffuse alopecia
  - No hirsutism
  - Post-inflammatory hyperpigmentation on face from acne
  - Acanthosis nigricans on neck, axillae, under breasts, groin

Case 2

26 yo woman

Routine labs:

- CBC WBC 11.8
- AST/ALT 46/65
- A1c 6.2
- Glucose 98
- Lipids TG 282, HDL 37, LDL 104
- TSH 4.59, free T4 0.9

Since she has missed periods:

- UHCG negative
- Prolactin 18
- Total T 60
- DHEAS 270

Case 2

The Plan

√ Reviewed the pathophysiology of PCOS

√ Reviewed the basic tools for becoming more sensitive to insulin

- Nutrition
- Physical activity
- Sleep

√ The role of insulin-sensitizing medications

√ Insulin-sensitizing supplements

Case 2

The Plan

1. No bleed for 3 months: medroxyprogesterone 10mg x 10 for a withdrawal bleed
2. Start metformin 500mg with a meal, taper weekly to 4 tablets if tolerated
   - ovulation may resume rapidly – consider OCP
3. Start 1mg vitamin B-12 (or calcium) to prevent B-12 malabsorption

Case 2 3 months after starting metformin

• BP	130/88	116/70
• WBC	11.8	5.4
• AST/ALT	46/65	14/22
• A1c	6.2	5.7
• TG	282	140
• HDL	37	43
• Total T	60	35
• DHEAS	270	190

Case 2 Take Home Points

- Started OCPs in teens before a diagnosis of PCOS
  - Delay diagnosis
  - Not able to take early steps to prevent complications
  - Progression of insulin resistance and β-cell dysfunction
- After d/c'ing OCP, most ovulate within 2 months
- Normal weight-PCOS exhibit metabolic dysfunction

Case 2 Take Home Points

- She had moderate alopecia – look at the scalp
- Not all women with PCOS are overweight
- Not all women with PCOS are hirsute
- She will not follow steps to improve insulin sensitivity if she doesn't understand the rationale

Case 3
46 year old woman with diabetes - History

- 46 year old woman moved to Philadelphia - needs a primary care
- Type 2 diabetes diagnosed 4 years ago
- Hypertension
- High cholesterol
- Overweight
- Difficulty conceiving, 1 pregnancy delivered via C-section
- 3 miscarriages, gestational diabetes
- Gall bladder surgery
- Mother had heart attack aged 53

Case 3
46 year old woman with diabetes - Medications

- Type 2 diabetes (used to take metformin TID)
  - Glipizide 10mg twice a day
- Hypertension
  - Lisinopril 40mg
  - HCTZ 25mg
- High cholesterol
  - Atorvastatin 40mg
- VMS - none

Case 3
46 year old woman with diabetes

- Vital Signs
  - Blood pressure 154/86
  - Height 5'4" Weight 207# BMI 35
- Physical Examination
  - Moderate alopecia
  - Severe facial hirsutism
  - No acne
  - Normal lungs, heart, abdomen
  - Multiple skin tags on neck
  - Acanthosis nigricans on neck, axillae, knuckles, elbows, knees

Case 3
46 year old woman with diabetes - studies

- Labs
  - Blood chemistry serum creatinine 1.1
  - Liver functions AST/ALT 44/62
  - Hemoglobin A1c 8.1
  - Blood count WBC 11.1 Hemoglobin 10.5
  - Triglycerides 350 LDL 223 HDL 36
  - Urine protein 45
- Additional labs
  - Vitamin B-12 283
- Liver ultrasound
  - Fatty infiltration of the liver

Case 3
46 year old woman with diabetes - Problem List

- Type 2 Diabetes: uncontrolled
- Uncontrolled Lipids: uncontrolled
- Decreased kidney function (serum creatinine and urine protein)
  - Stage 2 Chronic Kidney Disease with GFR 60
  - CKD G2/A2
- Non-alcoholic fatty liver disease (NAFLD)
- Anemia secondary to CKD
- Vitamin B-12 deficiency
- 10-year risk of MI: 7%. Lifetime risk: 50%

Case 3
46 yo woman with diabetes – Could this have been prevented?

- Irregular menses as a teen – "you'll grow out of it"
- Severe hirsutism – "it's an ethnic problem"
- Moderate alopecia – "it's hormonal"
- Gestational diabetes – "it's because you got pregnant when you overweight"
- Difficulty conceiving – "on BCP a long time," "come back in a year"
- BMI 35 – lack of education among other things – she said she was substituting "healthy wraps" for bread
- Mild anemia - "are you sure your periods aren't heavy?"
- Very high triglycerides – "cut back portions," "don't eat eggs"
- Never diagnosed with CKD ("your creatinine is within the normal range")
- Never diagnosed with NAFLD ("abnormal liver tests must be the cholesterol drug")

Case 3
46 yo woman with diabetes – Death by a thousand cuts.

- We must recognize signs & symptoms of PCOS at an early age.
- We must provide education and be our patients' advocates.
- We must believe what our patients tell us.
- We have to follow up abnormal blood tests.
- *There is absolutely no place for fat shaming.*

Case 4
Marquita – 27 year old woman

- Menarche 10, irregular intervals
- Severe acanthosis nigricans
- Severe alopecia
- Mild hirsutism
- A1c 6.5
- Hypertension
- 310#
- Very committed to diet and exercise, metformin, Victoza
- I insisted she be evaluated for sleep apnea – when she started CPAP, the weight melted off – she lost 70# in a year, A1c dropped to 5.7, off BP medication, only on metformin with monthly periods.