

Pre-Test Question #1

Polycystic ovary syndrome is

1. The most common cause of anovulatory infertility
2. Associated with a high rate of miscarriage
3. Associated with a high incidence of type 2 diabetes
4. All of the above

Pre-Test Question #2

Polycystic ovary syndrome is associated with

1. Endometrial carcinoma
2. Endometriosis
3. Ruptured ovarian cysts
4. All of the above

Pre-Test Question #3

*Initial* testing for irregular menses includes:

1. 24-hour Urinary Cortisol
2. TSH & Prolactin
3. 17-alpha-hydroxyprogesterone
4. All of the above

Pre-Test Question #4

Diagnostic criteria for PCOS include the following:

1. Irregular menstrual intervals
2. Signs of high androgens (hirsutism, alopecia)  
OR  
Elevated serum levels of androgens
3. Characteristic polycystic ovaries by ultrasound
4. All of the above

## PCOS

The intersection of sex hormones & metabolism

- Reproductive & endocrinologic features
  - Fueled by insulin resistance and androgens
- Prevalence ~10%
- A multi-factorial, polygenic disorder: variable phenotypes
- PCOS is under-diagnosed and under-treated
  - Multiple cardiovascular risk factors
  - High conversion to diabetes

## Definitions of 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

- Early
  - Irregular menstrual intervals
  - Hirsutism
  - Acne
  - Alopecia
  - Weight gain
- If presenting in late teens/early 20's - associated with a trigger:
  - Start or stop OCP; pregnancy
  - Gaining weight in college
  - Change in physical activity
- Later:
  - Dyslipidemia
  - IR/IGT/T2D
  - Hypertension
  - Fatty liver
  - Obstructive sleep apnea
  - Eating disorders
  - Endometrial carcinoma
  - DUB
  - Miscarriages, preterm births, stillbirth, gestational diabetes

## 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

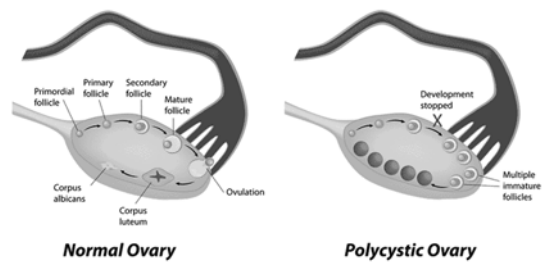
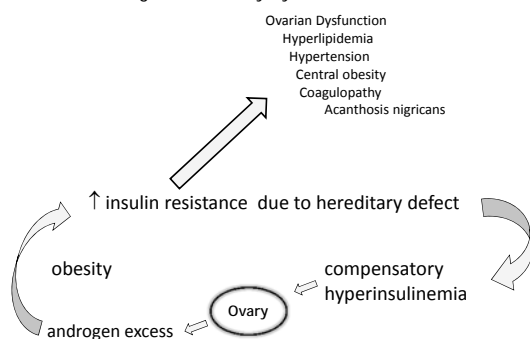
Qin JZ, Reprod Biol Endocrin 2013

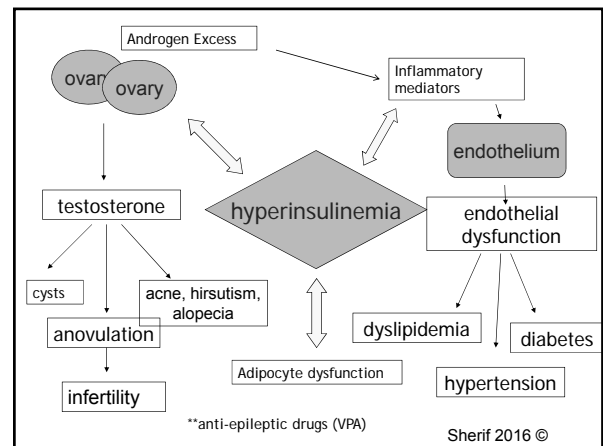
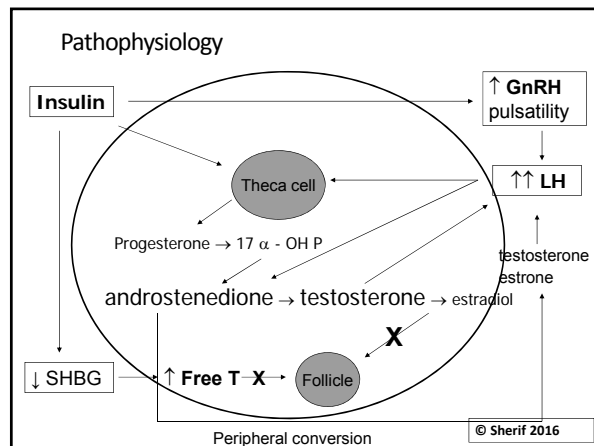
## It's not just about obesity.....

.....compared to age- & weight-matched controls

- PCOS women have higher prevalence & greater degree of hyperinsulinemia
  - *Clin Endocrinol Metab* 1987;65:499–507
  - *Diabetes* 1989;38:1165–1174
- PCOS women have more gestational diabetes (3.4x)
- 16% vs. 6% of PCOS develop diabetes at menopause
  - *Fertil Steril* 1992;57(3):505-13
- More OSA

## Insulin ↔ androgen ↔ obesity cycle





## History

- Abnormal menses:
  - Oligomenorrhea, amenorrhea, menorrhagia
- Reproductive abnormalities:
  - Infertility \*\*, multiple miscarriages, lactation disorder
- Endocrine disturbances:
  - Rapid weight gain, gestational diabetes, type 2 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)

## 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  $\alpha$ -OH progesterone
- If suspicion of Cushing's disease: 24<sup>h</sup> 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

#### Polycystic ovaries

- 10-12 *peripheral* cysts\*\*
- < 10mm diameter
- String of pearls
- Do not *rupture*
- Do not cause pain

#### Functional cysts

- In *stroma*, not periphery
- Larger than 1cm

\*\*arrested follicles

### Frequently observed lab abnormalities

- High TSH with normal free T<sub>4</sub>
- Elevated ALT & AST
- Elevated WBC's and CRP
- Dyslipidemia
  - High TG and low HDL

### Summary of Diagnosis: 2 out of 3

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<br>Hirsutism<br>Acne<br>Alopecia |
| • Anti-androgens             | Hirsutism<br>Alopecia                           |
| • Clomiphene                 | Infertility                                     |
| • Surgery (ovarian drilling) | Treats all symptoms                             |

### 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

### Management of Hirsutism, Alopecia, Cystic Acne

1. Start with OCP's first
    - If not enough improvement in 3-6 months, add anti-androgen
  2. If no OCP, or has been on one for a while and symptomatic,
    - Start anti-androgens, evaluate 3-6 months
- Anti-Androgens - teratogens
    - Androgen-receptor blockers
      - dose-dependent effect
    - 5-alpha-reductase inhibitors - Prevent conversion of T to DHT
    - Ornithine decarboxylase inhibitors: eflornithine
      - 30% response rate at six months

### Management of Hirsutism, Alopecia, Cystic Acne

- *Androgen-receptor blockers*
  - Spironolactone \*\* 50 or 100mg BID
    - 3-6 months for improvement, especially in alopecia
    - Don't use in CKD
  - Flutamide 250-500mg - Breast pain, dry skin, liver failure
- *5-alpha-reductase inhibitors*: finasteride 5 or 7.5mg
- Severe symptoms
  - Combine spironolactone and finasteride

\*\*spironolactone reduces androgens via 4 pathways

### Treat *insulin resistance* to improve reproductive, androgenic and metabolic problems

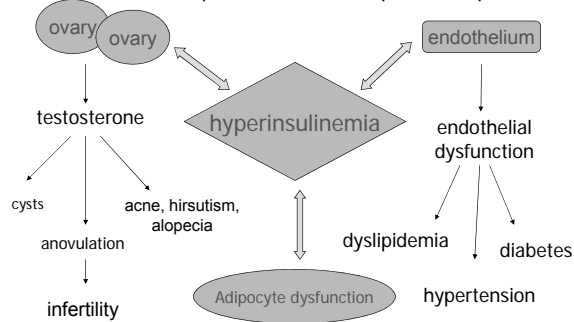
- Lifestyle
  - Nutrition - PCOSnutrition.com
    - Decrease both calories & simple carbohydrates
  - Increase physical activity and muscle mass
  - Sleep 8 hours per night
- Insulin-sensitizing medication - the rationale for metformin
- Insulin-sensitizing supplements

### 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

### Insulin sensitizers improve metabolic & reproductive problems



Sherif 2006 ©

### Supplements with insulin-sensitizing properties

- Inositol
  - D - chiro inositol & myo-inositol
    - Ovasitol brand – theralogix.com
- Vitamin D (5K) (not Rx)
- N-acetyl cysteine 500mg
- Cinnamon
- Chromium 250mg TID
- Alpha lipoic acid
- Resveratrol
- Berberine

## Management

- Follow up in three months to evaluate
  - Weight
  - Adherence to diet and exercise
  - Menstrual periods
  - Alopecia, acne, hirsutism
  - \*\*must be on multivitamin due to possible B-12 deficiency\*\*
- PCOSnutrition.com
- PCOSChallenge.com
- Not useful: repeating TVS, repeating androgens, measuring insulin

## Management

- To conceive:
  - Continue metformin
  - STOP spironolactone for one month
  - Most will conceive on metformin within 3-6 months
  - Must take multivitamin at least to prevent B-12 deficiency
- Pregnancy:
  - 1-2g metformin will reduce miscarriage by 50%
  - Reduce incidence of gestational diabetes
  - May reduce preeclampsia, preterm
  - More likely to lactate

## Summary of Management

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

## 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

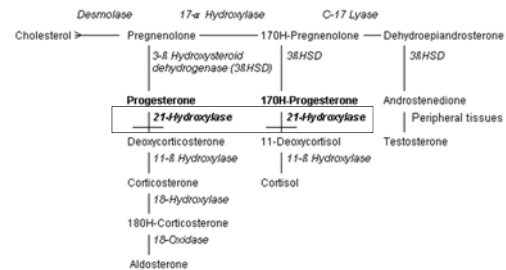
- 21-hydroxylase mutation impairs the ability of the adrenal gland to produce cortisol. In response, it works harder. When it works harder, it produces more androgens.
- Presents after puberty but many patients have clues early on:
  - Early menarche
  - Early breast development
  - Rapid growth in elementary 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 26 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  $\beta$ -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 T1D)
  - 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

#### 27 year old woman established care one year ago

- Menarche 10, irregular intervals
- Presents with amenorrhea for 2 years
- Not given medroxyprogesterone 10mg x 10 days
- Sexually active and never uses contraception
- Severe acanthosis nigricans
- Severe hirsutism
- No alopecia and mild cystic acne
- Blood pressure 150/98
- 310#

### Case 4

#### 27 year old woman established care one year ago

- Reviewed labs:
  - A1c 6.5
  - Transaminases in the 60’s
  - Triglycerides in 300’s
  - WBC 14.8
- Developed a plan:
  - Withdrawal bleed every three months with medroxyprogesterone 10mg x 10 days
  - Diet, exercise, sleep, metformin, liraglutide, spironolactone
- She was committed to the plan, but in six months, did not spontaneously menstruate and did not lose more than 10# in 6 months

Case 4

27 year old woman established care one year ago

- She downplayed her snoring and fatigue but agreed to sleep study.
- Diagnosed with sleep apnea and started BIPAP
- Continued same diet, exercise, sleep, metformin, liraglutide
- Within six months, the weight melted off, *with the same treatment*
  - She lost 70# (230#)
  - A1c dropped to 5.7
  - Menses resumed at 260#
  - All labs improved

Pre-Test Question #1

Polycystic ovary syndrome is

1. The most common cause of anovulatory infertility
2. Associated with a high rate of miscarriages
3. Associated with a high incidence of type 2 diabetes
4. All of the above

Answer: 4

Pre-Test Question #2

Polycystic ovary syndrome is associated with

1. Endometrial carcinoma
2. Endometriosis
3. Ruptured ovarian cysts
4. All of the above

Answer: 1

Pre-Test Question #3

*Initial* testing for irregular menses includes:

1. 24-hour Urinary Cortisol
2. TSH & Prolactin
3. 17-alpha-hydroxyprogesterone
4. All of the above

Answer: 2

Pre-Test Question #4

Diagnostic criteria for PCOS include the following:

1. Irregular menstrual intervals
2. Signs of high androgens (hirsutism, alopecia)  
OR  
Elevated serum levels of androgens
3. Characteristic polycystic ovaries by ultrasound
4. All of the above

Answer: 4