

# Nelson: PCOS from a GYN Perspective

## PCOS from a GYN Perspective

Anita L. Nelson, MD  
Harbor-UCLA Medical Center

## PCOS Conflict of Interest Disclosure Anita L. Nelson, MD

Research Grants	Bayer, Pfizer, Teva
Speakers Bureau	Bayer, Merck, Pfizer, Teva
Consultant, Advisory Board	Bayer, Ortho-McNeil, Pfizer, Teva

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 2

## PCOS Learning Objectives

At the end of this presentation, the participant will be able to:

- List the criteria for diagnosis of polycystic ovary syndrome (PCOS)
- Describe the underlying pathophysiology of PCOS
- Outline therapies for the different clinical problems associated with PCOS

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 3

## What Does "PCOS" Diagnosis Say?

- Is the women with PCOS always
  - ◆ Obese?
  - ◆ Hirsute?
- Does she always have
  - ◆ Infrequent menses?
  - ◆ Acne?
  - ◆ Insulin resistance?
  - ◆ Increased risks for CVD or DM?
- Common trait is infertility

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 4

## New Proposal: Consider PCOS as a "Modifier", not a condition requiring treatment

- Focus on actual problems in diagnosis
    - ◆ Obesity, with PCOS
    - OR
    - ◆ Hirsutism, with PCOS
    - OR
    - ◆ Anovulatory bleeding, with PCOS
  - Focus on treating actual problems
- Note: Routine use of Metformin to treat "PCOS" is not appropriate

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 5

## Prevalence of PCOS

- Most common endocrinopathy of reproductive-aged women
- Complete syndrome affects 5-10% of premenopausal women
- Functional androgen excess may affect up to 20% of reproductive-aged women
- Does not vary much by BMI
  - ◆ 8.2% in underweight women, 9.0% in obese women

Yildiz BO, et al. *JCEM*. 2008;93:162-68

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 6

## Nelson: PCOS from a GYN Perspective

### Prevalence of PCOS

- Most common endocrinopathy of reproductive-aged women
- Complete syndrome affects 5-10% of premenopausal women
- Functional androgen excess may affect up to 20% of reproductive-aged women

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 7

### Prevalence of PCOS

- 90% of women with oligomenorrhea have PCOS
  - ◆ 1/3 of women with secondary amenorrhea
  - ◆ 3/4 of women with anovulatory infertility
- Cross-cultural studies found PCOS prevalence rates are similar (Italy, Japan, US), but clinical manifestations differ

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 8

### Historical Definitions of PCOS

- 1935: Irving F. Stein and Michael Leventhal reported on 7 women with amenorrhea, hirsutism, and enlarged polycystic ovaries. Hence "polycystic ovary syndrome".
  - ◆ Postulated that thickened tunica prevented ovulation
  - ◆ Advocated wedge resection
- Later diagnostic criteria: oligomenorrhea, hirsutism, obesity with enlarged cystic ovaries

Anita L. Nelson, MD - 3/16/2010 09:00

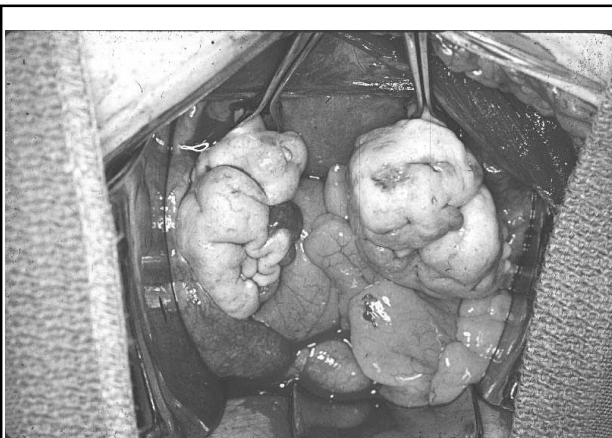
PCOS 04-08-10 Denver 9

### Gross Appearance of PCOS Ovary

- Gross surface area doubled
- Volume increased 2.8x
- Each ovary 20-100 cystic follicles
- Thickness of tunica increased 1.5x

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 10



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 11



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 12

## Nelson: PCOS from a GYN Perspective

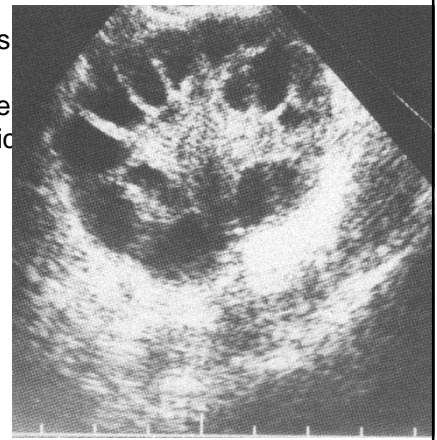
### Ultrasound: Polycystic Appearing Ovary (PAO)

- Consistent failure of follicle to grow beyond early antral stage
- “Black pearl necklace” ovary
  - ◆ Gross surface area doubled; volume increased 2.8x. Each ovary 20-100 cystic follicles. Thickness of tunica increased 1.5x
  - ◆ In single ultrasonographic plane, 12 peripherally oriented cysts measuring 2-9 mm diameter. Stroma usually 2x diameter of pericortical area. Ovarian volume increased > 10 ml

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 13

Small follicles are crowded at the surface of a polycystic appearing ovary



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 14

### Ultrasound Findings of PAO Do Not Identify a Specific Defect

- Any chronic anovulation causes PAO
  - ◆ 100% of congenital adrenal hyperplasia and female-to-male transsexuals
  - ◆ 75% of anovulatory women in randomized samples
- 16-23% of normal women have PAO on US
- 14% of OC users have PAO
- PAO can be found in children

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 15

### Gonadotropin Ratios Not Diagnostic

- Characteristics:
  - ◆ Mean luteinizing hormone (LH) concentrations higher
  - ◆ Follicle-stimulating hormones (FSH) low or normal
  - ◆ LH/FSH > 3; 2.5; 2
  - ◆ Bioactive LH elevation helpful
- Failings: only 70-75% of PCOS patients have abnormalities in gonadotrophins

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 16

### Gonadotropin Levels in PCOS

- Characteristics:
  - ◆ Mean luteinizing hormone (LH) higher
  - ◆ Follicle-stimulating hormone (FSH) low or normal
  - ◆ LH/FSH > 3; 2.5; 2
- **Not** used to diagnose PCOS
  - ◆ Only 70-75% of PCOS patients have abnormalities in gonadotrophins
- Bioactive LH elevation may be helpful

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 17

### Clinical Criteria for PCOS (NICHD 1990 Consensus)

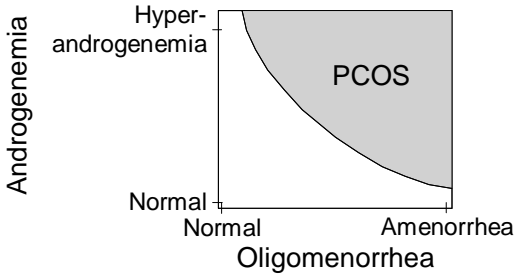
- Clinical evidence of hyperandrogenism (e.g. hirsutism, acne, androgenic alopecia) and/or hyperandrogenemia (e.g. elevated total or free testosterone)
- Oligo-ovulation (i.e. cycle duration > 35 days or < 8 cycles per year)
- Exclusion of related disorders (e.g. hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors, 21-hydroxylase-deficient non-classic adrenal hyperplasia)

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 18

# Nelson: PCOS from a GYN Perspective

## Arbitrary Demarcations Between Normal and PCOS Along Androgenemia and Oligomenorrhea Continua



Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 19

## Problems with 1990 Definition

- Similar ovarian dysfunction seen in hyperandrogenic women with
  - ◆ Regular cycles
    - 15% of these women are anovulatory
  - ◆ Ovulatory cycles

Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 20

## Revised 2003 PCOS Criteria (2 out of 3 Criteria)

1. Oligo-ovulation or anovulation
  2. Clinical and/or biochemical signs of hyperandrogenism
  3. Polycystic ovaries
- with**
- Exclusion of other etiologies: congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Fertil Steril.* 2004;81:19-25

Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 21

## Pathophysiology of PCOS

- No clear-cut etiology – multiple causes
- At-risk woman exposed to one or more insults may develop PCOS
  - ◆ Hypothalamic - pituitary dysfunction
  - ◆ Extraovarian androgen production
  - ◆ Ovarian dysfunction: androgen overproduction, estrogen underproduction, apoptosis dysfunction
  - ◆ Insulin resistance
  - ◆ Obesity
  - ◆ Calcium dysregulation

Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 25

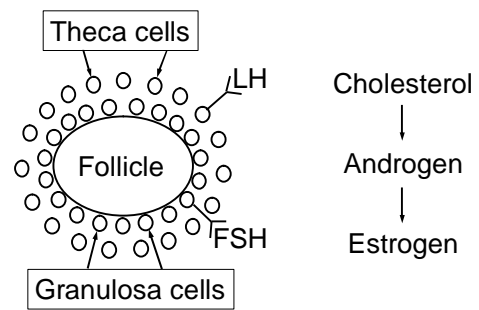
## Genetics of PCOS

- 50% of sisters of women with PCOS have hyperandrogenemia
- Twin studies: fasting insulin levels similar
- Caribbean-Hispanic women have twice the prevalence of PCOS compared to Caucasian women
  - ◆ Greater degree of insulin resistance found when matched for age and weight

Kauffman M. *JAAPA.* 2003;16:34-47

Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 26

## 2 Cell Hypothesis



Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 27

## Nelson: PCOS from a GYN Perspective

### Ovarian Contributions: PCOS Ovary

- Follicles do not progress beyond small antral phase
  - ◆ Androgen/estrogen ratio higher
- Apoptosis inhibited
- Follicles measuring 2-15 mm exist for months surrounded by hyperplastic thecal cells responsive to LH

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 28

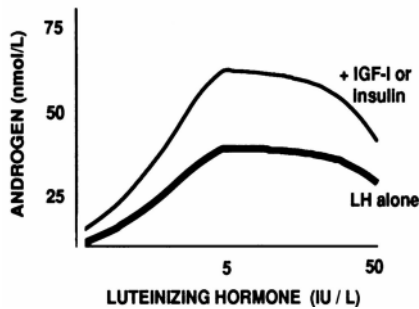
### Ovarian Contributions to PCOS: Monolayer Cell Preparation

- PCOS theca cells had increased androgen production per cell
  - ◆ P-450 C17 selectively increased androgen production, decreased progesterone production
  - ◆ Effects of growth factors (Insulin, IGF-1, IGF-2)
    - PCOS increased androgen basal levels and LH stimulation
    - No overlap between normal and PCOS preparation

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 29

### Model of LH-androgen Dose-response Curves



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 30

### Impact of Selective Insulin Resistance in PCOS

- Insulin resistance in skeletal muscle and adipose cells leads to hyperinsulinemia
- Hyperinsulinemia affects organs that retain insulin sensitivity
  - ◆ Hypothalamus → increases appetite  
→ increases GnRH
  - ◆ Adrenal → increases androgen production
  - ◆ Ovaries → increases androgen production
    - Decreases SHBG levels

Sozen I. *Obstet Gynecol Surv.* 2000;55:321-8

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 32

### PCOS Women Gain Regular Cycles with Ageing

- Ovarian ageing with follicle loss starts in utero
- Mathematical model shows gradual steady loss of follicles in cycling women until age 37
  - ◆ Accelerated rate of decline follows
- Survey of 205 PCOS women ≥ 30 years
  - ◆ Increase in % of women with regular cycles
    - Age 30-35 = 40%
    - Age 39-41 = 65%
  - ◆ New balance between inhibin B and FSH caused by follicle loss?

Elting M et al. *Human Reproduction.* 2000;15(1):24-8

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 36

### Adrenal Contributions Prevalence

- Significant proportion of women with hyperandrogenism also has excessive adrenocortical production
- DHEAS elevated more than 40-70% of PCOS
- Selective catheterization of hyperandrogenic women revealed that 12-42% had adrenal androgen hypersecretion of androstenedione (A4), dehydroepiandrosterone (DHEA), and 5-androstenediol (ADIOL)

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 38

## Nelson: PCOS from a GYN Perspective

### Hypothalamic Pituitary Dysfunction

- LH pulse amplitude and frequency higher in PCOS women
- Circadian pattern differences seen in both adults and teens (higher set point)
- GnRH pulsatility still abnormal when ovarian feedback removed
- Increase in LH – increases androgen symptoms
- Decrease in FSH – inhibits folliculogenesis

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 40

### Metabolic Syndrome Associated with Central Serotonergic Responsivity

- In humans, drugs that inhibit serotonergic neurotransmitters antagonize select 5-HT receptor subtypes and can
  - ◆ Alter mood, eating behaviors, locomotion activity, body temperature, body weight, and blood pressure
  - ◆ Induce insulin resistance

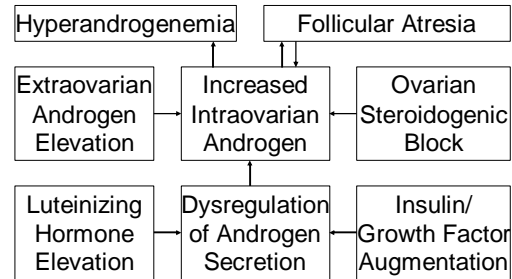
Muldoon MF, et al. *J Clin Endocrinol Metab.* 2006;91:718-21  
Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 42

### Hyperinsulinemia Normalized by Chronic Opioid Receptor Blockade in Hyperandrogenic Women

- Endogenous opioid peptides involved in insulin secretion and carbohydrate metabolism in hyperandrogenic
- Naltrexone 50 mg/d for ≥ 3 weeks
- Peripheral insulin sensitivity index improved from 30.76±1.43 to 33.69±1.78 (p<0.05)
- Insulin levels decreased in 75% of patients
- No change in BMI, LH, FSH, androgens or glucose level

Hadziomerovic D, et al. *Fertil Steril.* 2006;86(3):651-7  
Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 44

### Model of the Pathogenesis of Functional Ovarian Hyperandrogenism



Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 46

### Increased Risk of Type 2 Diabetes Mellitus

- Type 2 diabetes occurs at earlier age (20's-30's versus 50's-60's of general population)
- Due to insulin resistance (IR) and β-cell dysfunction
- PCOS women ages 14-44:
  - ◆ 31.1% have (undiagnosed) glucose intolerance
  - ◆ 7.5% have diabetes
  - ◆ Risk also exists for young and lean women
- PCOS women ages 40-59:
  - ◆ 15% have Type 2 diabetes

Goodarzi M. *Fertil Steril.* 2002;80:255-8  
Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 47

### Diabetes and IGT in PCOS

- 254 PCOS women (14-44 yrs) vs. 80 similar weight, ethnicity and age controls
- Family history and obesity in PCOS strong predictors
- Treatment of IGT may not be needed
  - ◆ FBS predicts cardiovascular diseases

	Normal Glucose	Intolerance	Type 2 DM
PCOS	61.4%	31.1%	7.5%
Controls	88.2%	10.3%	1.5%
PCOS (BMI > 27)	84.3%	15.7%	0%

Legro R, et al. *JCEM.* 1999;84(1):165-9  
Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 48

## Nelson: PCOS from a GYN Perspective

### PCOS: Association Between Sleep Disordered Breathing and Glucose Metabolism

- Prevalence of sleep disordered breathing in PCOS women 30-40 times than seen in age- and weight matched controls
- SDB is important risk factor for insulin resistance independent of BMI
- Insulin resistance was strong predictor of SDB in premenopausal women after controlling for age, BMI, free and total testosterone
- Lower sleep effectiveness, longer sleep latency and increased time awake
  - ◆ Chronic insufficient sleep

**Tasali E, et al. *J Clin Endocrinol Metab.* 2006;91(1):36-42**

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 49

### Endometrial Changes in PCOS

- Higher risk of hyperplasia in cancer
- Higher risk of spontaneous abortion
- Differences in endometrial steroid receptors and apoptosis receptors in PCOS versus normal women
  - ◆ Increased estrogen receptor  $\alpha$ , androgen receptors, suppressed expression of HOX10 gene in PCOS
  - ◆ Cell proliferation higher in epithelium of normals
  - ◆ Antiapoptotic proteins higher in PCOS
    - Bel-2 protein and bax mRNA expression

**Maliqueo M, et al. *Fertil Steril.* 2003;80 Suppl 2:812-9**

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 51

### PCOS and Cardiovascular Disease

- Markers for CVD higher in PCOS women
  - ◆ Evidence of higher mortality rates?
- 786 PCOS women (ovary biopsy) 30 year follow-up
  - ◆ No increased risk of CVD death
  - ◆ Nonfatal CVD events increased 3.4x
- 82,439 nurses – 14 year follow-up
  - ◆ Menstrual regularity vs. irregularity:
    - CHD RR 1.53 (95% CI 1.24-1.90) after adjustment for confounders
    - Absolute risk very low
  - ◆ Perhaps PCOS overtested/overtreated?

**Sattar N, Nelson S. *JCEM.* 2008 Jan;93(1):34-6**

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 55

### ACOG 2009 CVD in PCOS

- “An increased risk and early onset of cardiovascular disease in women with PCOS is strongly suspected but less well documented”
- Premenopausal women with PCOS have increased prevalence of subclinical atherosclerosis compared with controls

**ACOG Practice Bulletin No 108. *Obstet Gynecol.* 2009;114(4):936-49**

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 56

### Pregnancy Outcomes with PCOS

- Meta-analysis 720 PCOS vs. 4505 controls

Maternal risks increased	Odds Ratio	95% CI
Gestational diabetes	2.94	1.70 – 5.06
Pregnancy induced hypertension	3.67	1.98 – 6.81
Preeclampsia	3.47	1.95 – 6.17
Neonatal risks increased		
NICU admission	2.31	1.25 – 4.26
Perinatal mortality	3.07	1.03 – 9.21
Premature delivery	1.75	1.16 – 2.62

**Boomsma CM, et al. *Human Reprod Update.* 2006;12(6):673-83**

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 57

### IR Associated With Defects in Plasminogen Activator System

- Decreased proteolytic enzyme plasmin
- Plasmin important in clot lysis, ovulation and implantation
- Plasminogen → plasmin regulated by plasminogen activator inhibitor 1 (PAI-1), which is overproduced due to elevated insulin levels.
- PAI-1 levels and activity elevated in PCOS women, which may explain anovulation and implantation problem

Antia L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 58

## Nelson: PCOS from a GYN Perspective

### Caloric Thriftiness in PCOS

- 14 PCOS (7 lean & 7 obese) compared to 14 eumenorrheic matched controls
- Metabolic rate measured by continuous indirect calorimetry and insulin resistance (IR) by insulin tolerance test
- Resting energy expenditure did not differ between PCOS women and controls
- Postprandial (diet-induced) thermogenesis **reduced** in PCOS women
  - ◆ May predispose PCOS women to weight gain

Robinson S, et al. *Clin Endocrinol (Oxf)*. 1992;36(6):537-43

Anita L. Nelson, MD - 3/16/2010 09:00 PCOS 04-08-10 Denver 59

### Pathogenesis of PCOS

- In a **low fuel** milieu, PCOS might confer resistance to "metabolic anovulation"
  - ◆ ↑ GnRH drive is slowed to permit folliculogenesis
  - ◆ Historically, a low fuel milieu was imposed (starvation) rather than elected (dieting)
- In a **normal or high fuel** milieu, women with PCOS develop insulin resistance and anovulation
  - ◆ Reduced diet-induced thermogenesis
  - ◆ Caloric "thriftiness"

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 60

### Does PCOS Confer Advantages?

- Food deprivation hypothesis
  - ◆ Increased ovulation with seasonal weight loss
- Refeeding hypothesis
  - ◆ Preferential early ovulation with refeeding
    - Excessive response to ovarian stimulation
- Transgenerational privation hypothesis
  - ◆ Androgenic anabolic state improves use of food for protein synthesis and fat storage
  - ◆ Helps fetal and newborn survival
  - ◆ Helps adult survival and reproductive capacity

Shaw LMA. *BJOG*. 2008;114:4-8

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 61

### Recognition of PCOS

- Recognition of patient with PCOS is important to prevent long-term sequelae of PCOS
- Traditionally, care has been fragmented among specialists, but need to be alert that one symptom suggests others

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 62

### Clinical Features of PCOS in US Women

Clinical Features	Prevalence
Oligo-ovulation	>90%
Hirsutism	70-80%
Polycystic ovaries	70-80%
Android obesity	50-60%
Androgenic alopecia	20-25%
Acne	15-25%

Farah L, Azziz R. *The Female Patient*. 1999;24:79-85

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 63

### Androgen Disorders?

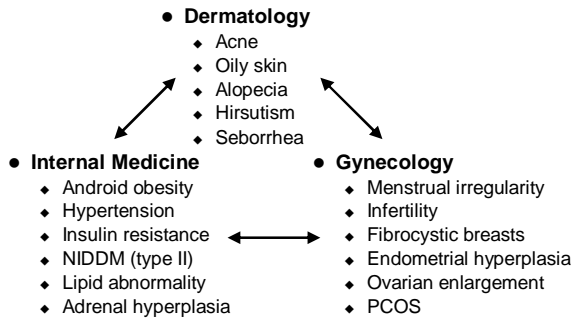


Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 64

## Nelson: PCOS from a GYN Perspective

### If You Find One Androgen Sign, Look For More



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 68

### Endocrinologic Features of PCOS in US Women

Endocrinologic Features	Prevalence
Decreased SHBG	60-80%
Elevated free testosterone	40-70%
Elevated androstenedione	40-60%
LH/FSH > 3	40-50%
Elevated DHEAS	30-60%
Elevated total testosterone	20-50%

Farah L, Azziz R. *The Female Patient*. 1999;24:79-85

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 69

### ACOG 2009 Clinical Manifestations of PCOS

- Menstrual disorders
- Infertility
  - ◆ Ovarian hyperstimulation syndrome
  - ◆ Multifetal pregnancy
  - ◆ Gestational diabetes and hypertension
- Skin disorders
  - ◆ Hirsutism, acne, androgenic alopecia
- Insulin resistance
  - ◆ Metabolic syndrome; nonalcoholic fatty liver disease, sleep apnea
- Endometrial cancer risk factors (but not cancer?)
- Mood disturbances and depression

ACOG Practice Bulletin No 108. *Obstet Gynecol*. 2009;114(4):936-49

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 72

### ACOG 2009 Differential Diagnosis

- Androgen secreting tumor
- Exogenous androgens
- Cushing syndrome
- Nonclassical congenital adrenal hyperplasia
- Acromegaly
- Genetic defects in insulin action
- Primary hypothalamic amenorrhea
- Primary ovarian failure
- Thyroid disease
- Prolactin disorder

ACOG Practice Bulletin No 108. *Obstet Gynecol*. 2009;114(4):936-49

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 73

### Workup for PCOS

- Personal history
- Family history of endocrine, reproductive, metabolic disorders
- Physical examination
- Laboratory tests

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 75

### Workup for PCOS: Personal History

- Weight over lifetime, especially menarche, time of onset of menstrual irregularity, recent patterns
- Hirsutism: onset and progression, any treatments used
- Menstrual history: menarche, interval, duration, mittelschmerz, premenstrual molimina, changes over time

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 76

## Nelson: PCOS from a GYN Perspective

### Workup for PCOS: Personal History

- Obstetric history and complications (e.g. gestational diabetes)
- Medications, especially androgenic or anabolic drugs and dilantin
- Changes in voice
- Known medical problems
- Surgeries
- Symptoms of clinical depression

Anita L. Nelson, MD - 3/16/2010 09:00

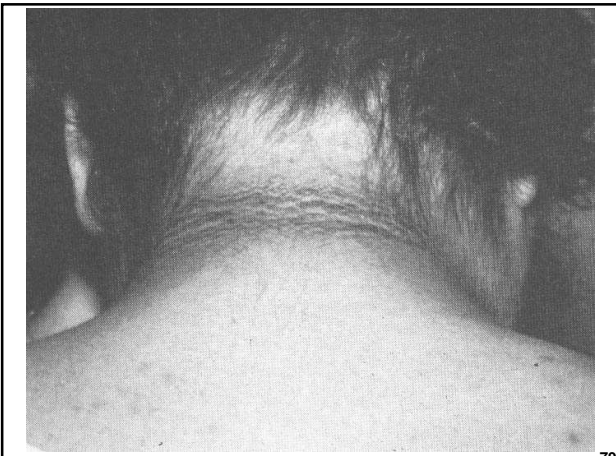
PCOS 04-08-10 Denver 77

### Workup for PCOS: Physical Exam

- Blood pressure
- Height, weight, BMI, waist circumference
- Acne: severity, distribution (face, chest, back)
- Alopecia/male pattern baldness
- Excessive hair growth: type, pattern, hirsutism score (Ferriman-Gallwey score possible)
- Acanthosis nigricans
- Thyroid enlargement or nodularity
- Galactorrhea

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 78



Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 79

### Workup for PCOS: Physical Exam

- Pelvic/abdominal masses
- Clitoromegaly
- Coarseness of facial features
- Enlarged hands or feet
- Cushingoid feature
- Signs of systemic diseases

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 80

### Workup for PCOS: Laboratory Tests

- TSH: routine
- PRO, if unexplained spontaneous galactorrhea
- Testosterone, DHEAS for minimally hirsute women or women with worsening hirsutism
- Glucose testing options
  - ◆ Fasting versus 2HGTT
- AM 17-hydroxyprogesterone in follicular phase if indicated
- Transvaginal ultrasound only if indicated

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 84

### Laboratory Tests: Hirsute Women Not Seeking Pregnancy

- Testosterone
  - ◆ Free Testosterone
    - Equilibrium dialysis
    - Ammonium sulfate precipitation
- Free T index
- Total T not very sensitive
  - ◆ Most common test
- DHEA-S only if hirsutism rapidly progressive
- 17-OHP in young women
- Ultrasound only if indicated

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 86

## Nelson: PCOS from a GYN Perspective

### Laboratory Tests: Mildly Hirsute or Non Hirsute Women Not Seeking Pregnancy

- ◆ TSH
- ◆ Prolatin if unexplained spontaneous galactorrhea
  - Many PCOS have mild elevations
- ◆ Glucose testing (all PCOS vs. risk factor)
  - 2HGTT vs. Fasting
- ◆ FSH and E<sub>2</sub> if prolonged amenorrhea
- ◆ Ultrasound only if indicated

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 87

### ACOG 2009 Screening for Diabetes in PCOS

- FBS + 2 hour glucose after 75 g load
  - ◆ 2-5 fold increased risk of DM
  - ◆ 40% PCOS have glucose intolerance
- No recommended screening test for insulin resistance
  - ◆ Little utility to routine testing of insulin levels in women with PCOS
    - Does not predict who will respond to therapy

ACOG Practice Bulletin No 108. *Obstet Gynecol.* 2009;114(4):936-49  
Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 91

### Criteria for Metabolic Syndrome in Women with PCOS (3 out of 5)

Risk Factor	Cutoff
Abdominal obesity	> 88 cm (> 35 in)
Triglycerides	> 150 mg/dL
HDL-C	< 50 mg/dL
Blood pressure	> 130 / > 85
Fasting glucose	> 100 mg/dL

Grundy SM, et al. *Circulation.* 2005;112:285-90

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 92

### Individualizing Testing for PCOS

- 13 year old with menarche 4 months ago
- Has acne and has had only one period since then

What work up does she need?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 95

### Individualizing Testing for PCOS

- 17 year old with menarche age 11 and sexual debut at age 16
- Menses unpredictable
- Occur with no moliminal symptoms every 2-4 months and last 2-8 days
- BMI = 27 Mild Acne. Upper lip has some extra hair growth. No spontaneous galactorrhea

What tests would you offer her?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 96

### Individualizing Testing for PCOS

- 18 year old with menarche age 14
- Menses 2-3 times a year lasting 1-2 days
- Marked hirsutism on face, chest and back is progressively worsening
- Moderate acne

What tests would you offer her?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 97

## Nelson: PCOS from a GYN Perspective

### Individualizing Testing for PCOS

- 34 year old G<sub>3</sub>P<sub>3</sub> obese woman who reports that since her post partum tubal ligation, her menses have become “irregular”. Upon questioning, she admits to gaining 50 pounds with her last pregnancy, 40 of which she has not lost. Also had gestational diabetes.

What tests would you offer her?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 98

### Individualizing Testing for PCOS

- 38 year old with history of normal monthly menses until about a year ago.
- No menses in last 4 months.
- Rapidly worsening facial hair. Shaves 3 times a day.
- Deep voice.
- Temporal baldness.

What tests would you offer her?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 99

### Individualizing Testing for PCOS

- 29 year old G<sub>0</sub> woman with BMI = 37 with life long history of infrequent menses.
- Sexually active with proven partner for 4 years without conception.
- No history of STDs.
- No spontaneous galactorrhea.
- Desires fertility ASAP.

What tests would you offer her?

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 100

### PCOS: Overall Goals of Treatment

- Reduce production and circulating levels of androgens
- Protect endometrium from unopposed estrogen
- Achieve normal body weight
- Lower risk for cardiovascular disease
- Avoid hyperinsulinemia's effects on CVD and DM
- Plan and prepare for pregnancies

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 103

### Treatments for PCOS

- Patient and health care provider must decide goals of therapy
- Preventive health
  - ◆ Weight loss
    - Very low caloric intake needed to achieve weight loss <sup>1</sup>
  - ◆ Exercise

1. Kiddy DS, et al. *Clin Endocrinol (Oxf)*. 1992;36:105-11

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 104

### What Can Weight Loss Accomplish for PCOS Women?

- Normalizes ovulation
- Reduce total and free androgen levels
  - ◆ Improve clinical signs of hyperandrogenemia
- Reduce visceral fat which decreases
  - ◆ Insulin resistance
  - ◆ Hyperglycemia
  - ◆ Lipid disorders

Panadis D, et al. *Fertility and Sterility*. 2008 Apr;89(4):899-906

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 106

## Nelson: PCOS from a GYN Perspective

### ACOG 2009 CVD Prevention in PCOS

- Lifestyle modifications are the best approach to modify risks for cardiovascular disease and diabetes
- Calorie restriction rather than composition of diet itself
- Recent studies have suggested little benefit to the addition of Metformin above lifestyle therapy alone
- Data are insufficient to recommend insulin – sensitizing agents prophylactically to prevent diabetes in women with PCOS

ACOG Practice Bulletin No 108. *Obstet Gynecol.* 2009;114(4):936-49

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 107

### Which Diet is Best?

- Impact of caloric restriction rated by whether sugars or fats were preferentially restricted **despite equivalent weight loss**
- Low glycemic, high fat diet yielded better biochemical outcomes than high glycemic, low fat
  - ◆ Lower insulin resistance
  - ◆ Lower BP, triglycerides, and C-reactive protein
- High fat, low glycemic diet preserved BMR while low fat, high glycemic diet decreased BMR
- **High fat diet associated with better well-being**
- **Not specifically tested in women with PCOS**

Pereira MA, et al. *JAMA.* 2004;292(20):2482-90

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 108

### Orlistat: 54 Week Trial in Obese Adolescents

- Dose: Orlistat 120 mg 3 times daily vs placebo

	Orlistat	Placebo
BMI	-0.55	+0.31
Weight (Kg)	+0.53	+3.14
Waist circumference (cm)	-1.33	+0.12

Chanoine JP, et al. *JAMA.* 2005;293:2873-83

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 110

### Orlistat vs Metformin in PCOS

- Metformin 500 mg 3 times daily (n = 11)
- Orlistat 120 mg 3 times daily (n = 10)
- Weight reduction
  - ◆ Metformin: 1.0%
  - ◆ Orlistat: 4.7%
- Compliance equal (~90%)
- Testosterone levels dropped in both groups
- No change seen in SHBG, fasting insulin levels or lipid profiles

Jayagopal V, et al. *J Clin Endocrinol Metab.* 2005;90:729-33

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 112

### Treatments for PCOS: Anovulatory Cycling

- Combination hormonal contraceptives: OCs, patches or vaginal rings
  - ◆ Cyclic, extended-cycle or continuous use
  - ◆ May not be appropriate for obese women over age 35
- Cyclic progestin (MPA, NETA)
  - ◆ Initiate 12-day therapy PRN no menses for 30-35 days
- Chronic progestin: DMPA, POPs, LNG-IUS

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 114

### Treatments for PCOS: Androgen Excess

- Acne and hirsutism
  - ◆ Combination hormonal contraceptives or
  - ◆ GnRH agonists with estrogen-progestin add back
- Hirsutism
  - ◆ Spironolactone
  - ◆ Finasteride
  - ◆ Vaniqa
  - ◆ Electrolysis or laser

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 116

## Nelson: PCOS from a GYN Perspective

### Treatment Recommendation IGT

- Treat hypertension as diabetes (<130/<80)
- Treat lipids as diabetic
  - ◆ LDL-C <100
  - ◆ Watch for niacin and glucose
- ASA daily unless contraindicated
- Lifestyle: diet low in total, saturated fat and transfatty acids
- Glycemic meds for:
  - ◆ IFG + IGT +/- metabolic syndrome, worsening glycemia, CVD, GDM, NA fatty liver disease, PCOS

American College of Endocrinology Consensus Statement on the Diagnosis and Management of Pre-Diabetes. July 23, 2008

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver119

### ACOG 2009 Infertility Treatments in PCOS

- First line treatment for ovulation induction: clomiphene citrate
- Second line
  - ◆ Low does gonadotropin
  - ◆ Ovarian drilling
  - ◆ Aromatase inhibitors
  - ◆ Add Metformin to clomiphene citrate

ACOG Practice Bulletin No 108. *Obstet Gynecol.* **2009**;114(4):936-49

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver120

### Metformin for Induction of Ovulation

- Non-obese PCOS women in a 6-month trial
  - ◆ Clomiphene 150 mg cycle days 3-7
  - ◆ Metformin 850 mg 2 times daily

	Clomiphene	Metformin
Pregnancy rate	34%	69%
Spontaneous abortion rate	38%	10%

Palomba S, et al. *J Clin Endocrinol Metab.* **2005**;90(7):4068-74

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver121

### Clomiphene, Metformin or Both for Infertility in PCOS

	Clomiphene	Metformin*	Both
N	209	208	209
% Ovulation	49.0	29.0	60.4
% Pregnancy	23.9	8.7	31.1
% Live birth	22.5	7.2	26.8

\* Extended release metformin

Legro RS, et al. *N Engl J Med.* **2007**;356(6):551-66

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver122

### Predicting Response to Metformin for Ovulation

- Polymorphism in *STK11*
  - ◆ Kinase gene expression in liver
  - ◆ Site of metformin action
- Women with C/C or C/G instead of G/G
  - ◆ Only 53-60% the ovulations per cycle
- Ovulation rates also lower for metformin
  - ◆ Heavier women
  - ◆ Longer infertility
  - ◆ Higher free androgen index

Legro RS, et al. *JCEM.* **2008**;93(3):792-800

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver123

### Aromatase Inhibitors

- Progestin-induced withdrawal bleed
- Agents used cycle days 3-7
  - ◆ Letrozole 2.5 mg daily
  - ◆ Anastrozole 1 mg daily
  - ◆ Exemestane 2.5 mg daily
- Letrozole vs anastrozole
  - ◆ Ovulation rates: 84% vs 60%
  - ◆ Pregnancy rates: 27% vs 17%
- Multiple gestation rates lower than with clomiphene

Barbieri RL. *OBG Management.* **2005** Oct:12-14

Antia L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver124

## Nelson: PCOS from a GYN Perspective

### Treatments for PCOS: Infertility

- Laparoscopic ovarian drilling
  - ◆ Ovarian drilling increases ovulatory cycling and pregnancy with cumulative conception rates of 54% at 12 months and 72% at 24 months <sup>1</sup>
  - ◆ Ovarian drilling does not change insulin levels, insulin sensitivity, or serum vascular endothelium growth factor levels <sup>2</sup>

1. **Felemban A**, et al. *Fertil Steril*. 2000;73:266-9
2. **Tulandi T**, et al. *Fertil Steril*. 2000;74:585-8

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 125

### Consensus on Infertility Treatment Related to PCOS

- Weight reduction and exercise
- Preconceptional counseling, smoking, alcohol
- Ovulation induction
  1. Clomiphene citrate
  2. Exogenous gonadotropins OR Laparoscopic ovarian surgery
  3. IVF
- Metformin use for infertility treatment in PCOS should be restricted to women with glucose intolerance

**Consensus on Infertility Treatment.** *Fertil and Steril*. 2008;89(3):505-21

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 126

### New Proposal: Consider PCOS as a "Modifier", not a condition requiring treatment

- Focus on actual problems in diagnosis
  - ◆ Obesity, with PCOS  
OR
  - ◆ Hirsutism, with PCOS  
OR
  - ◆ Anovulatory bleeding, with PCOS
- Focus on treating actual problems

Note: Routine use of Metformin to treat "PCOS" is not appropriate

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 127

### ASRM Recommendations Treatment for PCOS

- Lifestyle modification with diet and exercise are first line treatment of all PCOS, especially those with increased BMI
- Routine use of insulin-sensitizing agents in women with PCOS is **not** warranted for the long-term prevention of diseases
- Add insulin-sensitizing agent after diagnosis of IGT if diet and exercise alone are not effective

Practice Committee of American Society for Reproductive Medicine. *Fertil Steril*. 2008; 90,Suppl 3:S69-73

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 128

### PCOS Web Sites

- **Hormone Foundation:**  
<http://www.hormone.org>
- **Polycystic Ovarian Syndrome Association:**  
<http://www.pcosupport.org>
- **American College of Obstetricians and Gynecologists:**  
<http://www.acog.org>

Anita L. Nelson, MD - 3/16/2010 09:00

PCOS 04-08-10 Denver 129