

POLYCYSTIC OVARY SYNDROME (PCOS)

New Perspectives

*Michel Abou Abdallah, MD.
Reproductive Endocrinology*

Learning Objectives

At the conclusion of this presentation, participants should be able to:

- Appreciate the spectrum of clinical presentations of PCOS
- Appreciate the breadth of health implications of PCOS
- Initiate a diagnostic workup & rule out conditions that mimic PCOS
- Individualize risk assessment and tailor management strategies
- Become familiar with emerging concepts in the field

PCOS Demographics

- **Prevalence:**

- > 5-10% of premenopausal women

- Geographical and racial disparity?

- Obese versus lean phenotype

Clinical Presentation

- **Ovulatory**

- Disturbance**

- > Oligomenorrhea
 - > Amenorrhea
 - > Meno-metrorrhagia

- **Hyperandrogenism**

- > Hirsutism
 - > Acne
 - > Alopecia

- **PCO**

- **Diagnosis of Exclusion**

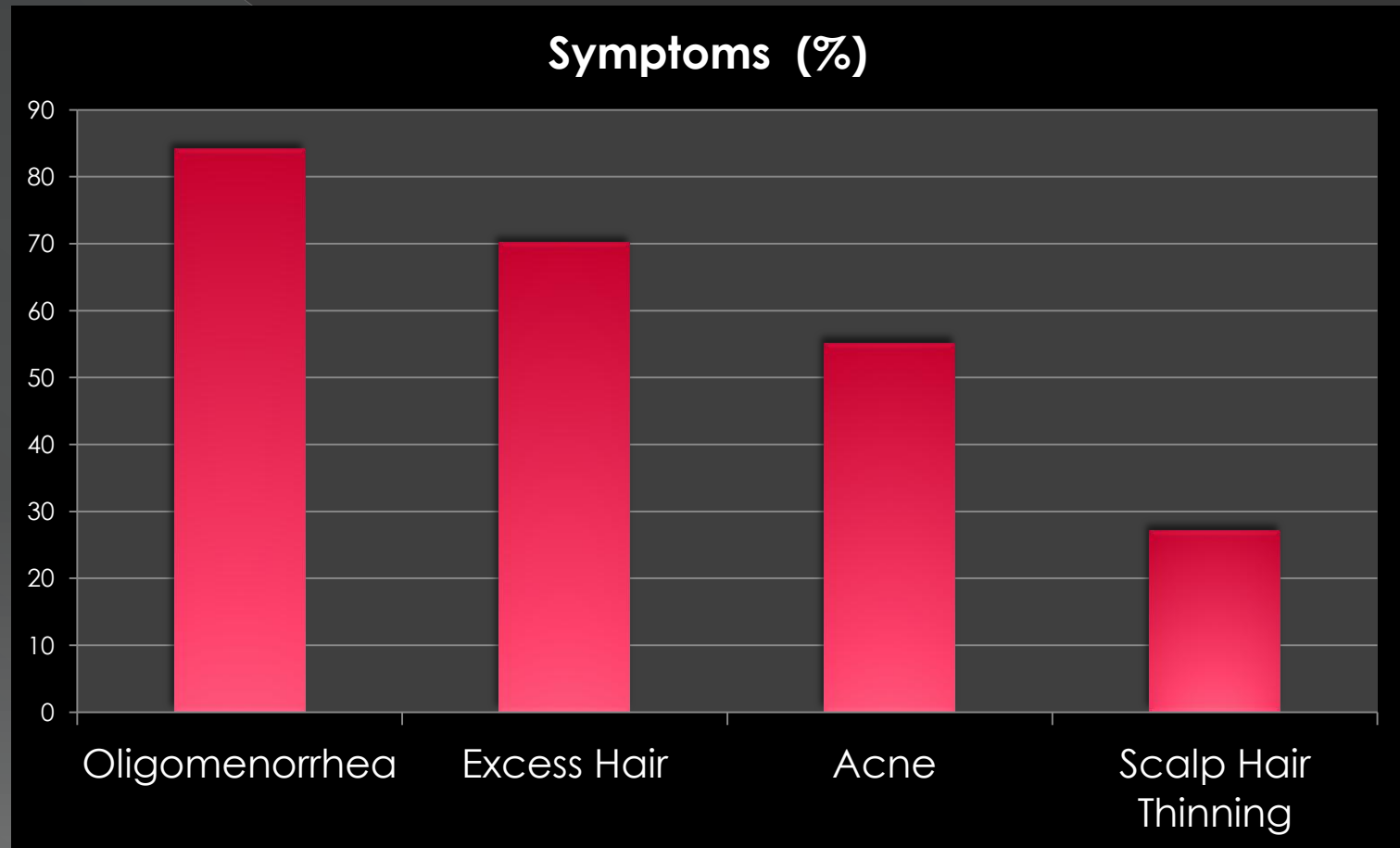
- Premature adrenarche

- Early onset puberty

- Fertility

- > Infertility
 - > Subfertility

Common Symptoms of PCOS (n=263)

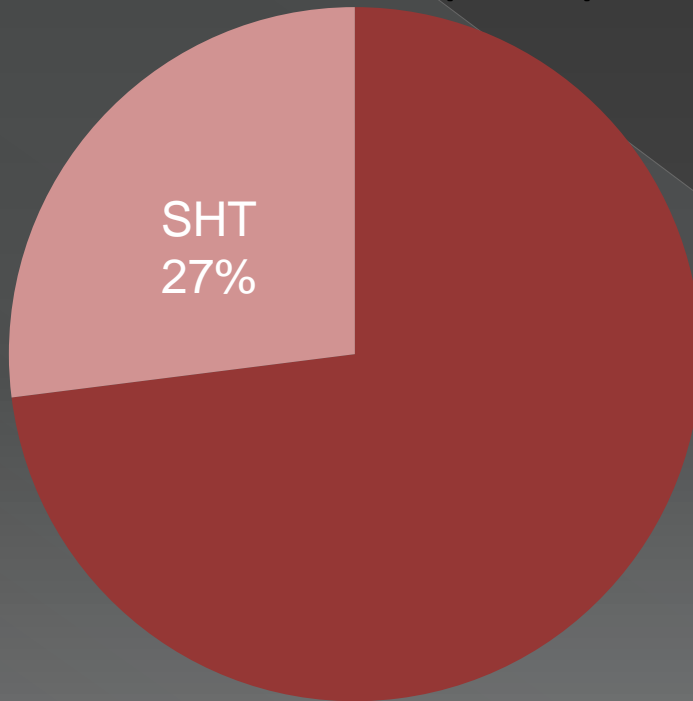


Mean age: 28.6 (SD 6) years
Mean BMI: 33 (SD 9) kg/m²

Pal L. Unpublished

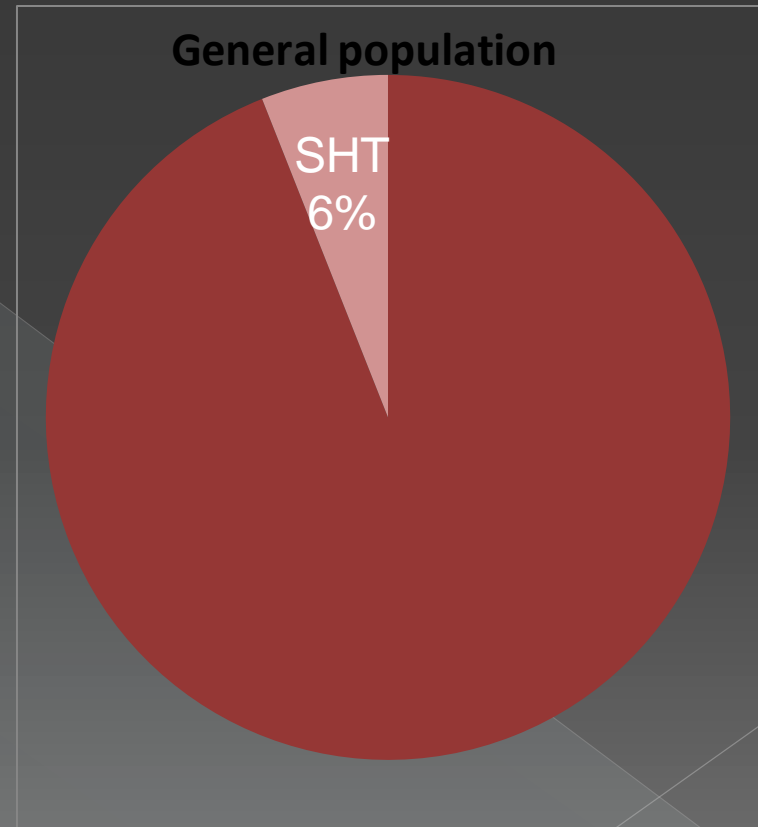
Scalp Hair Thinning (SHT) – a common symptom of PCOS

Women with PCOS (N=263)



Ikhena D et al. ASRM 2013 Annual Meeting

General population



Birch MP et al. BR J Dermatol 2001;144:297-304

Milieu of PCOS

ENDOCRINE

- Hyperandrogenemia
 - Ovarian
 - Adrenal
 - Androgen Metabolites
- Altered FSH:LH ratio
- Prolactin excess?

METABOLIC

- Hyperinsulinemia
- Abnormal glucose homeostasis
- Dyslipidemia
 - > Low HDL
 - > Elevated TG
- Pro-inflammatory
- Hyper-homocystenemia?

Causative Mechanisms... *still unclear*

- **Hypothalamic dysfunction**

- > GnRH pulsatility

- **Pituitary dysfunction**

- > Altered FSH:LH
- > Altered LH pulsatility
- > Hyperprolactinemia

- **Adrenal dysfunction**

- > Excess adrenal androgens

- **Ovarian dysfunction**

- > Theca cell
 - Excess ovarian androgens
- > **Granulosa cell**
 - Elevated AMH

- Metabolic underpinnings

- > Insulin resistance

- Genetic disorder

- > Heritability

- **Epigenetic disorder**

- > IUGR/SGA
- > Maternal obesity
- > GDM

PCOS Diagnostic Classifications

Symptoms/ Signs	NIH 1990	Rotterdam 2003	AES 2006
Oligomenorrhea ^a	+	+/-	+/-
Hyperandrogenism ^b	+/-	+/-	+/-
Hyperandrogenemia	+/-	+/-	+/-
PCO on US ^c	-	+/-	+/-
Diagnostic Criteria	Oligomenorrhea <i>plus</i> androgen excess	Any <i>two</i> of the above criteria	Ovulation related concerns <i>plus</i> androgen excess

^a 8 or less menses per year

^b Acne or hirsutism or androgenic alopecia

^c Ovarian volume >10ml and/or > 12 follicles <9mm in size in at least one ovary

Health Concerns

⦿ **Infertility**

- > Multiples
- > OHSS
- > Miscarriage
- > Complications of pregnancy
 - GDM
 - Macrosomia

⦿ **Risk for Progeny**

⦿ **Gynecological**

- > DUB
- > Endometrial pathology
- ⦿ CVD
- ⦿ Stroke
- ⦿ **Diabetes**
- ⦿ **Depression**
- ⦿ **Cancer**
- ⦿ **All cause mortality**

Evaluation

⦿ Clinical

- > History
- > Exam
 - BMI/WC/NC
 - Objective hirsutism
 - Severity & distribution of acne/hair loss
 - Hallmarks of IR?
 - Acanthosis nigricans
 - Skin tags
- > Pelvic ultrasound
 - PCO
 - **Endometrial echo**

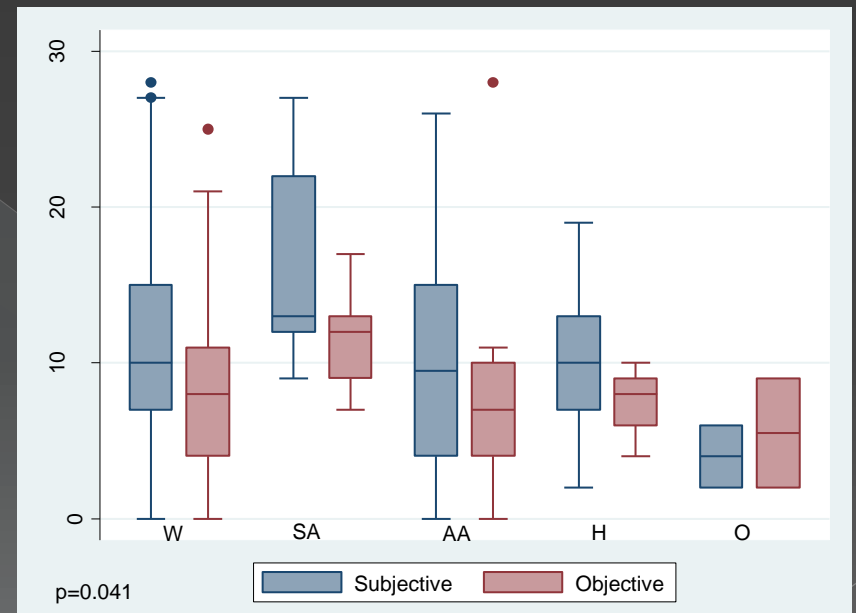
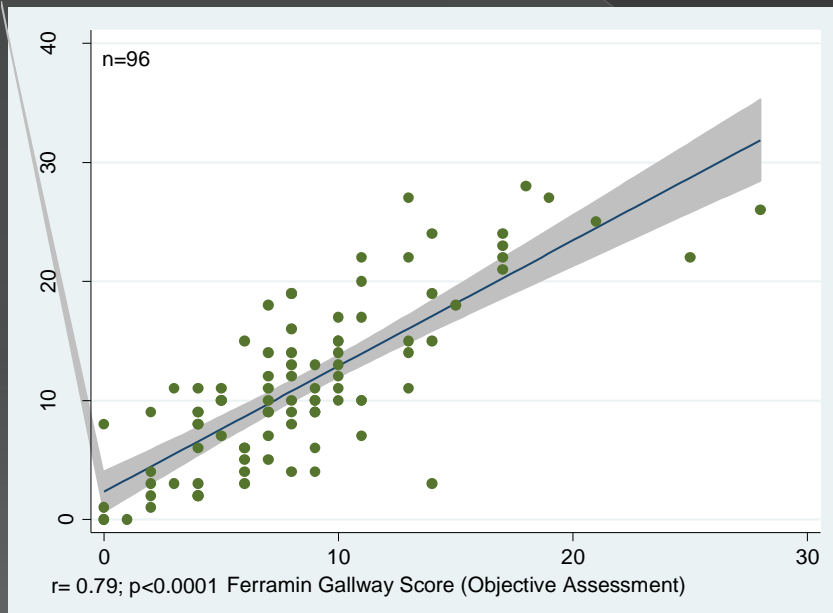
⦿ Rule out....

- > Thyroid disorder
- > Hyperprolactinemia
- > Late onset CAH
- > Cushing Syndrome
- > Androgen secreting tumor

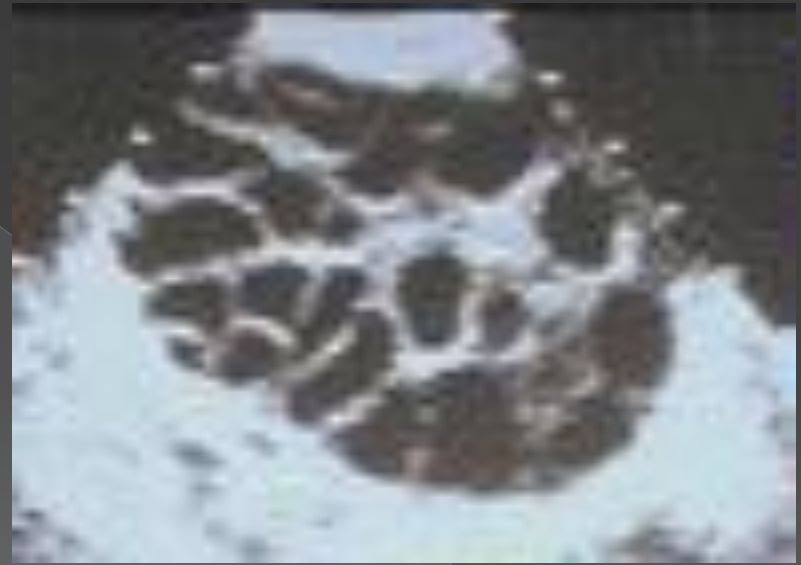
⦿ Assess risks

- > Diabetes/ CVD
- > Depression
- > Endometrial cancer
- > Pregnancy related

Subjective Quantification of Hair Excess Using FG Score



Polycystic Ovarian Morphology



>12 non-growing follicles <9mm in a single ovary
Ovarian volume >10mm³

Ovarian stromal density relates to degree of insulin resistance and hyperandrogenemia

Investigations

- **Pelvic US**

- **Androgens**

- Total/Free T

- DHEAS

- Androstenedione

- 3 α AG

- FSH/LH/E2

- Prolactin

- TSH

- **17OH Progesterone**

- 17OH Pregnenolone

- AMH

- Fasting Lipids

- OGTT (75 gm)

- *25OH Vitamin D*

- **Miscellaneous**

- > 24 hr. UFC

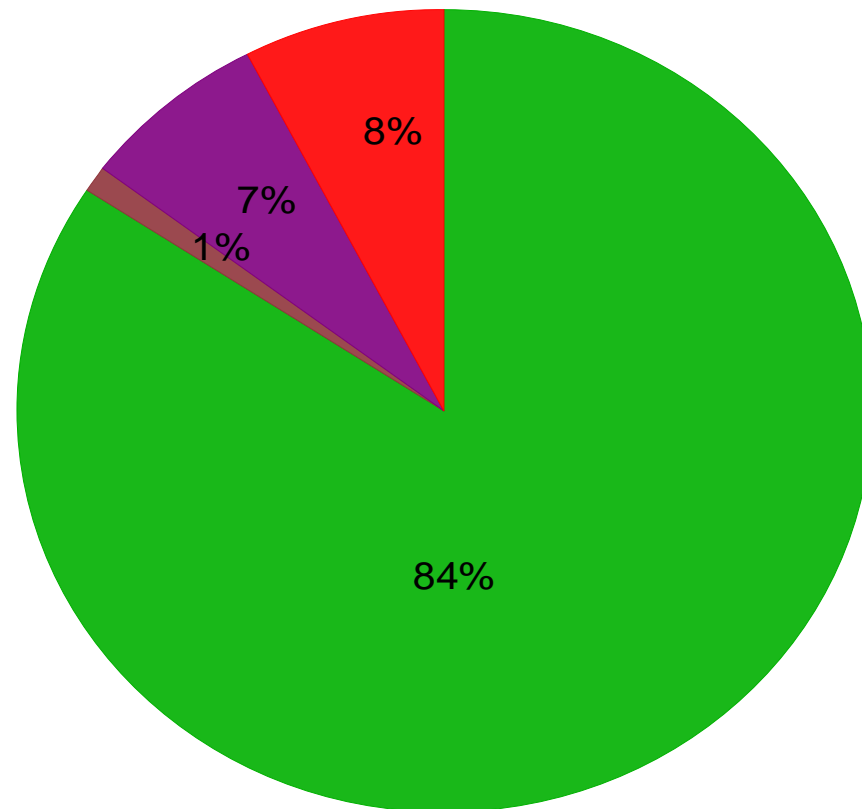
- > C-Reactive Protein

- > Homocysteine

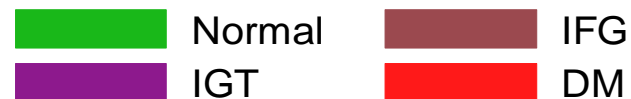
- > **Endometrial biopsy**

Glucose Metabolism in PCOS

Glycemic Status of Women with PCOS (n=197)



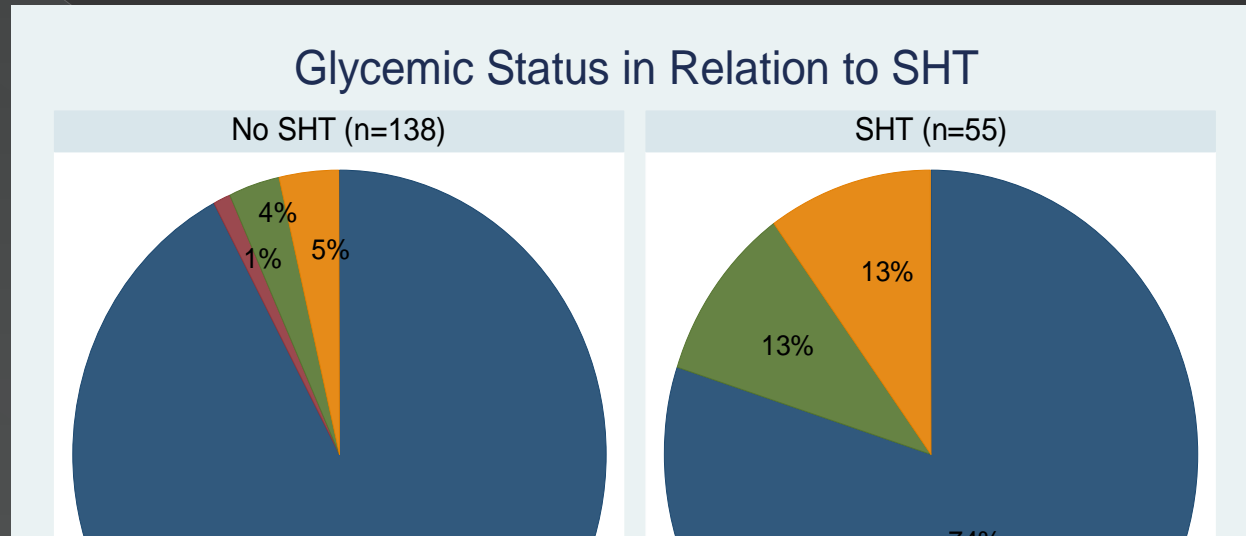
Mean age: 26 ± 6 years
Mean BMI: 34 ± 9 kg/m²



The Dx of metabolic syndrome requires 3 of the following 5 clinical characteristics

1. Increased waist circumference
2. Increased blood pressure (≥ 130 mmHg systolic , ≥ 85 mm Hg diastolic)
3. Increased triglycerides (dyslipidemia)
4. Decreased HDL-cholesterol (< 50 mg/dl)
5. Increased fasting glucose (≥ 100 mg/dl) or previously established diabetes mellitus

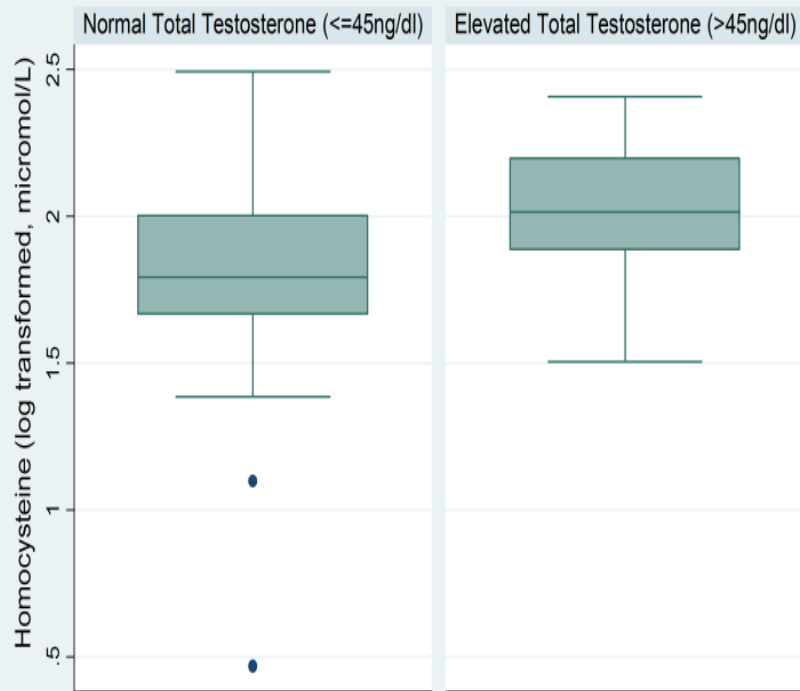
OGTT Response in Women with PCOS c/o Scalp Hair Thinning (SHT)



Women with PCOS who acknowledge SHT are significantly more likely to manifest IGT or DM on OGTT compared to those without this

Homocysteine, Insulin Resistance & Hyperandrogenemia

Elevated Homocysteine in Women with Hyperandrogenemia



Two tailed $p=0.024$

Higher homocysteine levels with worsening insulin resistance



$r: -0.41, p=0.004$

Insulin Resistance

Compensatory Hyperinsulinemia

Progressive decline in
pancreatic β cell
reserve

Glucose intolerance

DM T2

Chronic low grade inflammation

↑ C-reactive
protein

↑ interleukin-6

↑ leucocyte
count

=

**Inflammatory
markers**

↑ plasminogen
activator
inhibitor Type 1
(PAI-1)

↑ Principal
Inhibitor of tissue
plasminogen
(+PA)

↑ Urokinase
=

**Inhibiting
Fibrinolysis**

- Obesity → aggravate the underlying insulin resistance
- Rate of progression from glucose intolerance to DM is ↑ up to 10% in PCOS women.
- Risk of DMT2 is ↑ 3-7 fold in women with PCOS

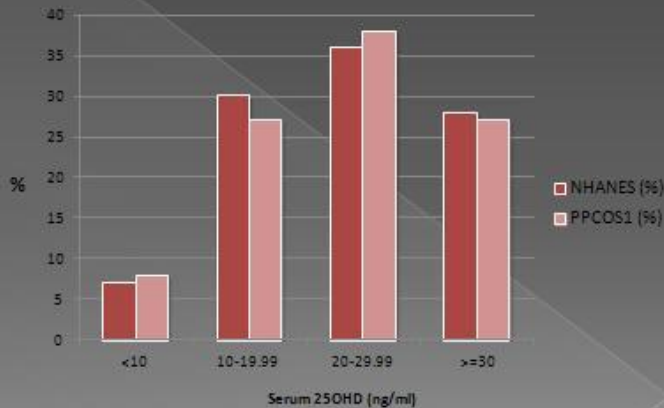
N.B. Metformin ↓ levels of c-reaction protein, & soluble vascular cellular adhesions molecules (sVCAM), (Alleviate chronic inflammation)

Vitamin D Deficiency & PCOS?

- Obesity
- Dyslipidemia
- Insulin resistance
- Pro-inflammatory milieu
- Diabetes and CVD
- Breast cancer
- Depression

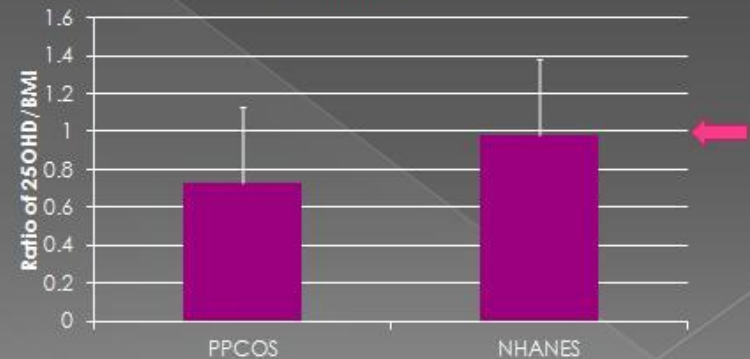
Vitamin D Status of Women with PCOS

Vitamin D level in women enrolled in PPCOS1 (n=540) & NHANES 2003-6 (n=1280)



P=0.136

Significantly Reduced serum 25OHD : BMI ratio in PPCOS1 compared to general US population



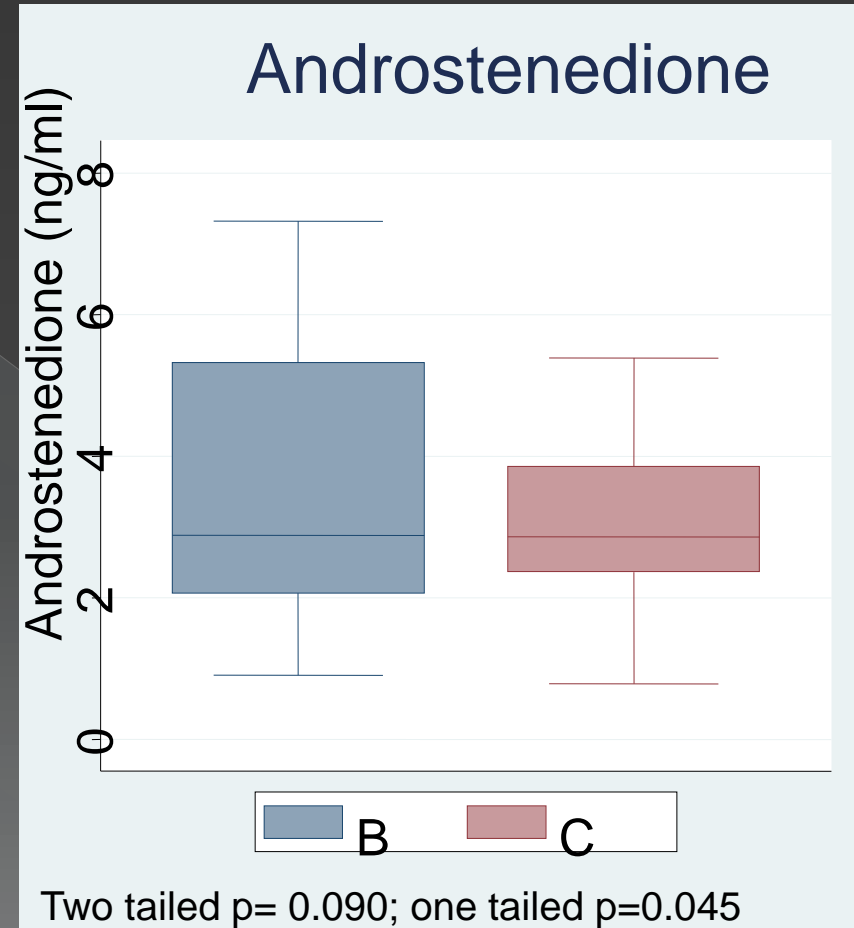
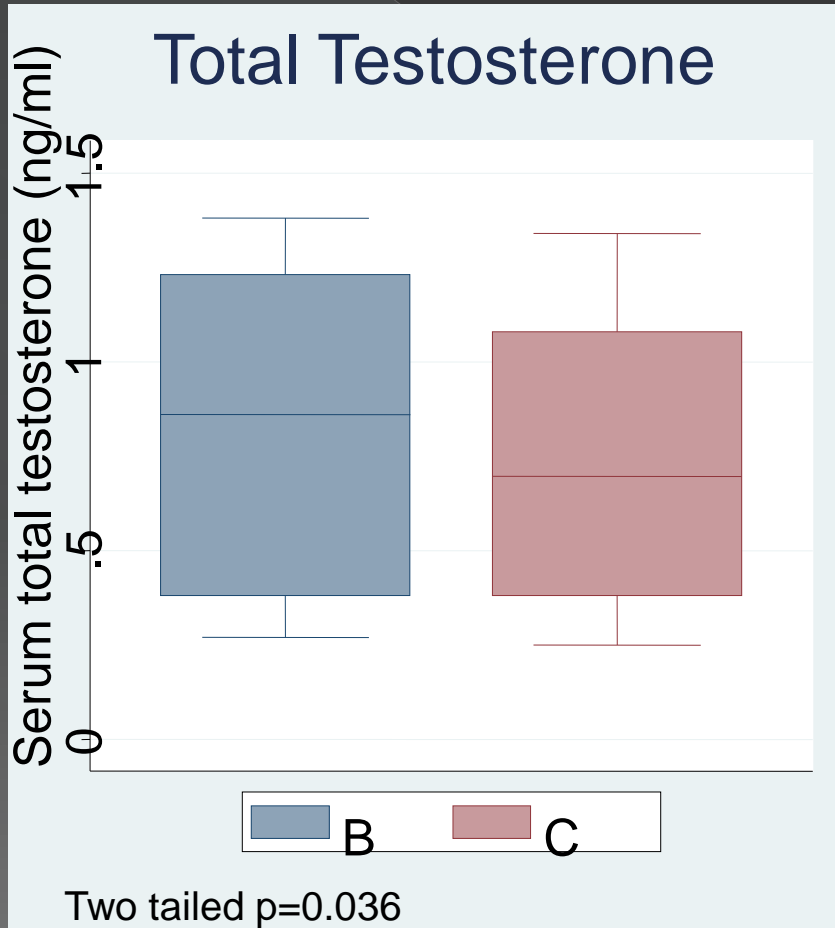
P<0.001

Reproductive Relevance of Vitamin D Status in PCOS?

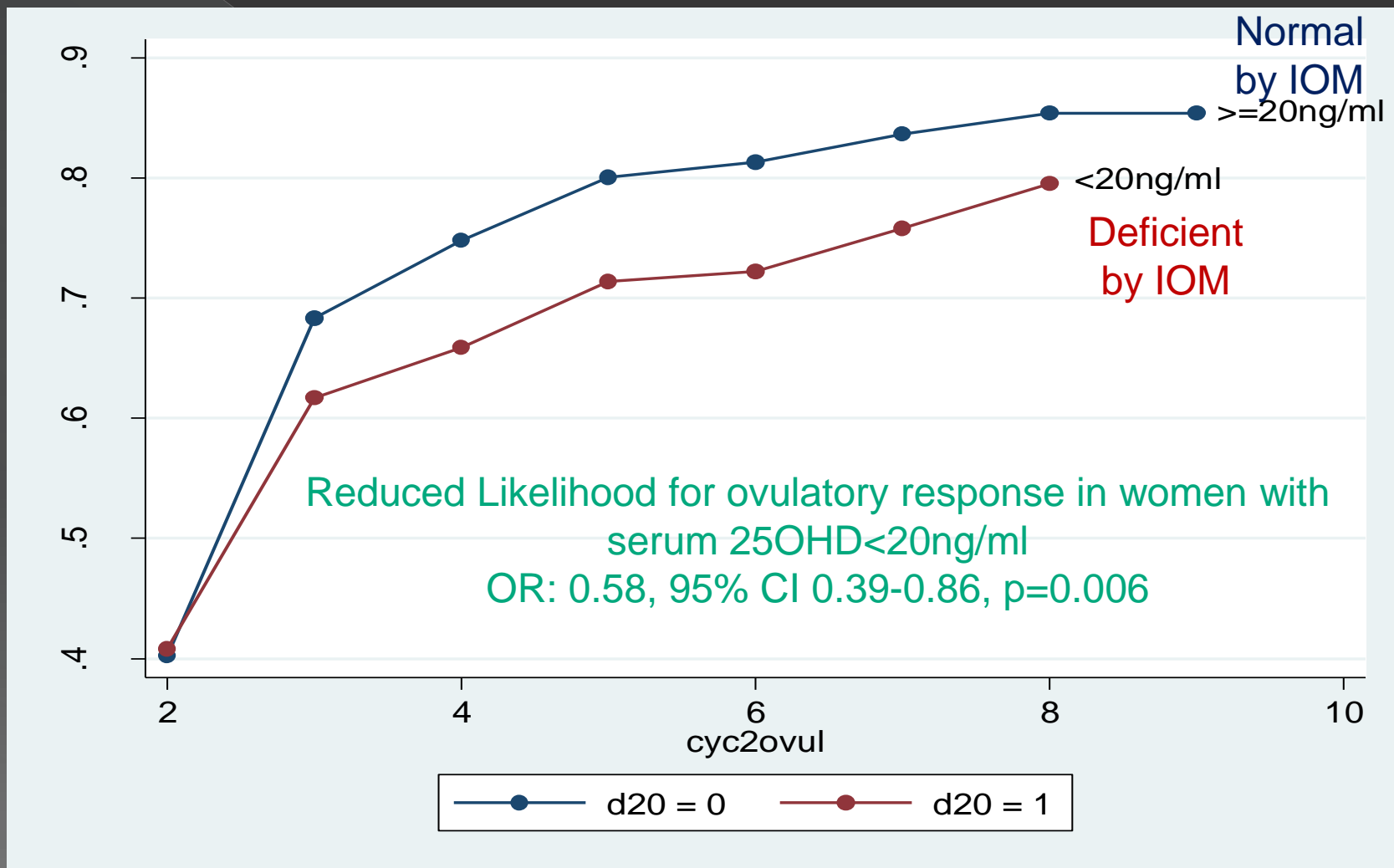
Hypothesis

- ⦿ Higher serum 25OHD levels will relate to an increased likelihood of fertility treatment success in women with PCOS
 - ⦿ Improved ovulatory response
 - ⦿ Improved live birth

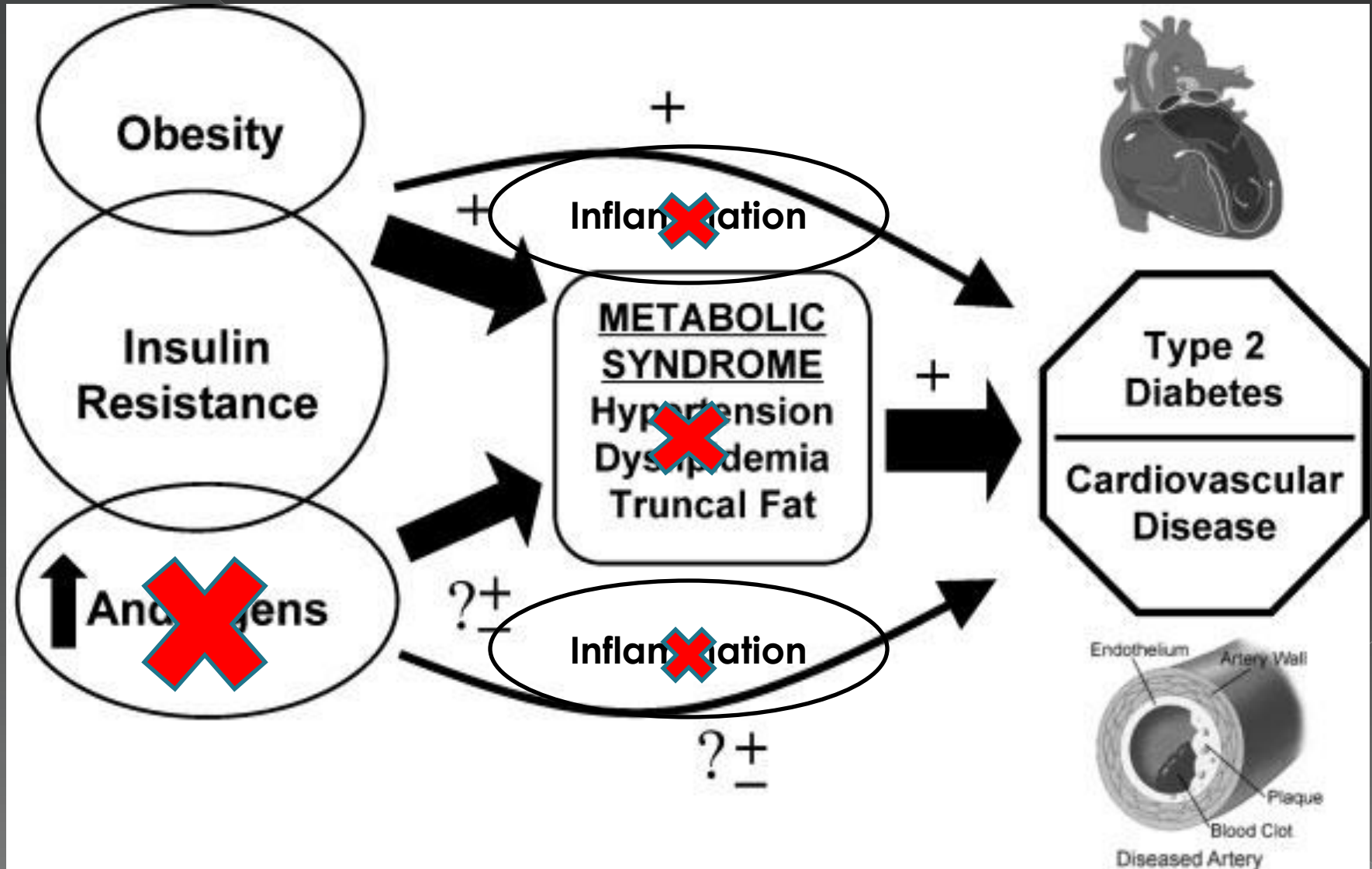
Improved Androgen Profile with Vitamin D & Ca Rx.



Vitamin D Status Predicts Ovulatory Response in CC & M users

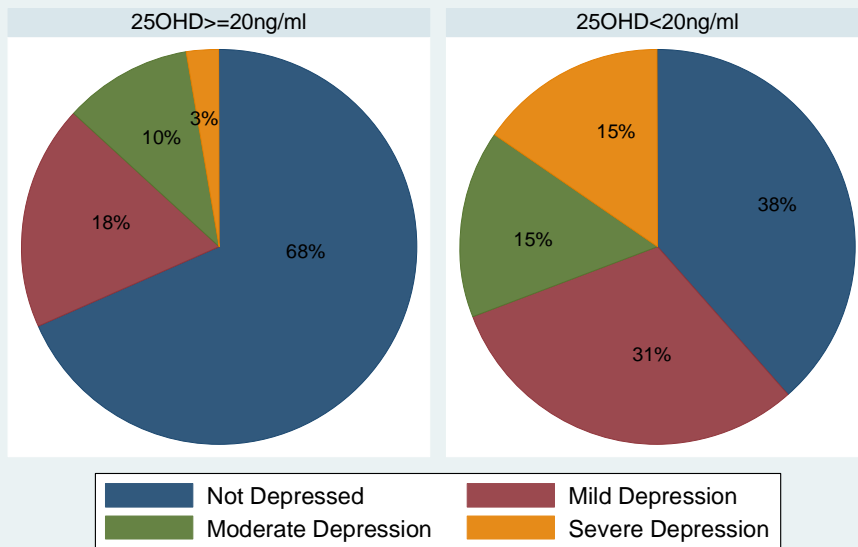


Cardioprotective Implications of Vitamin D for Women With PCOS



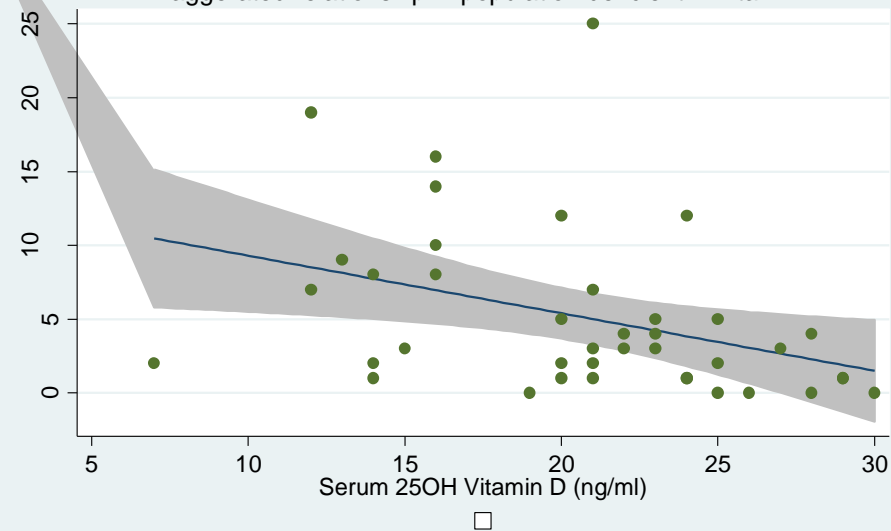
D-Status & Depression in PCOS

Vitamin D Deficiency & Depressive Symptoms in PCOS



p=0.045

Correlation b/w PHQ score & Serum 25OHD
Exaggerated relationship in population deficient in vitamin D



r = - 0.45 p=0.003

Wrap Up

1. Vitamin D deficiency is highly prevalent
2. *Importance of Vitamin D for health is established*
3. *Improved fertility treatment success is noted in women with normal vitamin D status*
4. Maternal vitamin D status has implications for fetal & neonatal wellbeing
5. Goal of supplementation should be to achieve normalization of vitamin D status through combination of supplements and lifestyle.

Symptom Specific Approach

Hyperandrogenism

- OCP
- Anti-androgen Rx
 - > AR blocker
 - > 5 α reductase inhibitor
- Ornithine decarboxylase inhibitor
- Insulin sensitizers
- Statins
- Glucocorticoids
- Vitamin D
- Myoinositol
- Depilatory strategies

Menstrual issues

- Combined hormonal contraceptives (CHC)
 - > Oral
 - > Vaginal
 - > Transdermal
- Progestin only
 - > Oral
 - > IM
 - > IUD
 - > Subcutaneous

Choice of CHC- *Considerations*

- Contraceptive needs?
- Degree & nature of hyperandrogenism
- Risk profile
 - > Migraines?
 - > Hypertriglyceridemia?
 - > Gall stones?
- Dose of EE
- Route of EE
 - > Oral/TV/TD
- Compliance?

Progestin

- Androgenic potential
- Anti-androgenic
- Risk profile
 - > Metabolic
 - > Mood/ affect
- Route
 - > Oral/IM/SQ/IUD

PCOS Related Infertility

Rule out other contributors

Ovulation Induction

- Clomid
- **Aromatase Inhibitors (Letrozole)-PPCOSII**
- Gonadotropins
- Ovarian Drilling
- *Ovarian Wedge resection?*

IVF

- GnRH antagonist
- GnRH agonist trigger
 - > Metformin

IVM

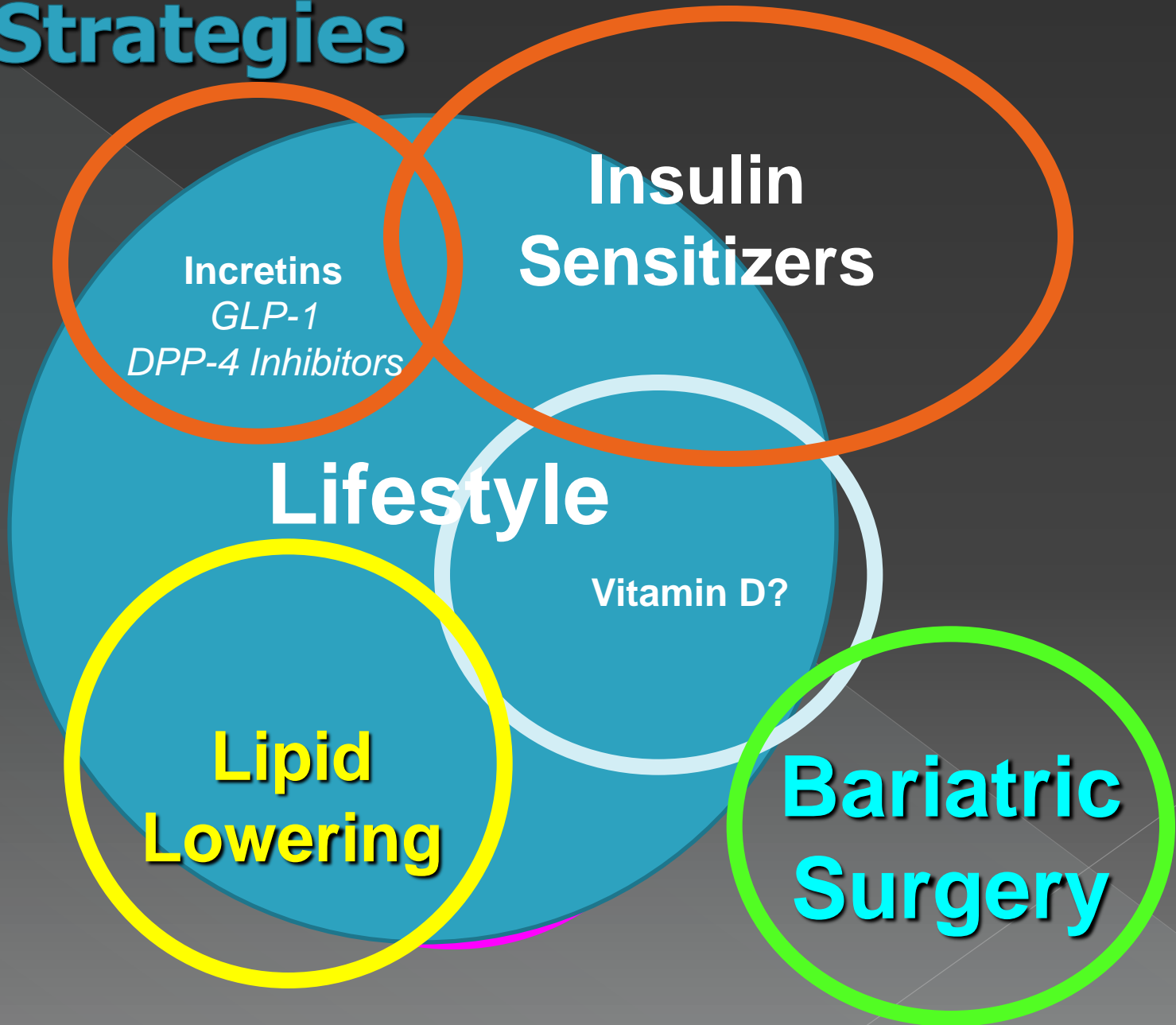
Adjunct

- Insulin sensitizer
- Psychological support
- **Vitamin D**
- *Myoinositol*

Endometrial Risk Reduction

- Combined Hormonal Contraceptive
- Progestin alone
 - > Regimen
 - > Route
 - > Dose
- Metformin ?
- Endometrial surveillance

CVD & DM Risk Reduction Strategies



Management Summary

- **Remember - PCOS is a diagnosis of exclusion**

- **Prioritize Mx goals**

- **Quantify risks**

- > Endometrial
- > DM
- > CVD
- > Depression
- > Infertility

- Initiate preventive strategies

- **Optimize lifestyle**

- > Diet

- > Physical activity

- **Choice & Rx urgency should be dictated by patient's needs & prioritized goals**

Conclusion

PCOS is a polygenic disorder likely involving the interaction of numerous genomic variants and the influence of environmental factors.

Candidate genes include all the molecules that participate in the affected metabolic & reproductive pathways.

Conclusion:

We clearly are in a new era in our understanding & management of women with PCOS.

Conclusion:

In the past, we treated the specific problems of **infertility**, **dysfunctional uterine bleeding**, and **hirsutism** effectively.

Conclusion:

We now have the opportunity,
indeed the obligation,
to offer interventions that can help prevent
or reverse some of the metabolic
consequences of the disorder that have an
important impact on overall health and on
the quality & quantity of life.

Take Home Points:

- ⦿ PCOS is COMMON
- ⦿ PCOS is A HETEROGENEOUS disorder
- ⦿ Diagnosis has LONG TERM health implications for the patient & her progeny
- ⦿ A HOLISTIC approach to PCOS management should include attention to overt symptoms as well as covert risks.