Objectives

- Introduction
  - Introduce background statistics of PCOS
  - Review the diagnosis of PCOS
  - Summarize the evaluation of PCOS
- PCOS & obesity
  - Explore PCOS related metabolic disturbances
  - Explain the relationship between androgens & obesity
- Conclusions & summary
Background

- PCOS is a complex endocrine disorder affecting women of childbearing age characterized by increased androgen production and ovulatory dysfunction.
- PCOS is the leading cause of anovulatory infertility and hirsutism.
- Women with PCOS have an increased risk of miscarriage, insulin resistance, hyperlipidemia, type 2 diabetes, cardiovascular disease, and endometrial cancer.

There is no uniform definition for PCOS.
- PCOS describes a diverse and heterogeneous group of women.
- PCOS is a syndrome and not a disease.
- PCOS is prevalent.
  - 5-10% women in US are affected.
- PCOS is not cured but instead requires management of symptoms, risk factors & co-morbidities.

Background

- PCOS imparts a significant health care-related economic burden.
- Diagnostic evaluation is only ~ 2% of the cost.
- Screening for the disorder appears be a cost-effective strategy → earlier diagnosis, intervention → prevention of serious sequelae

<table>
<thead>
<tr>
<th>Annual cost in millions of US dollars (% of total)</th>
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<tbody>
<tr>
<td><strong>Initial evaluation</strong></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td><strong>Menstrual dysfunction/AUB</strong></td>
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<tr>
<td><strong>Infertility</strong></td>
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<tr>
<td><strong>DM type 2</strong></td>
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<tr>
<td><strong>Hirsutism</strong></td>
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<tr>
<td><strong>Total cost</strong></td>
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Diagnosis

- PCOS was initially described in 1935 by Irvin Stein & Michael Leventhal as *syndrome* based on a case study of 7 women with:
  - Obesity
  - Infertility with amenorrhea
  - Hirsutism
  - Polycystic ovaries
- These are still in part considered characteristic but not consistently found in all women with PCOS.

Diagnosis

- Diagnostic criteria has changed and evolved over time.
- Many different professional medical groups have offered guidelines.
- PCOS may be managed by many different medical specialties:
  - Pediatricians/Internists/Family practice
  - Dermatologists
  - OB/GYN, reproductive endocrinologists
  - Endocrinologists

Evaluation

<table>
<thead>
<tr>
<th>History</th>
<th>Physical</th>
<th>Laboratory</th>
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<tbody>
<tr>
<td>Pubertal age/sexual development</td>
<td>Vitals (BP, BMI, waist circumference)</td>
<td>Pregnancy test</td>
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<tr>
<td>Menstrual history (menarche, menstrual pattern)</td>
<td>Cutaneous manifestations (acne, hirsutism, acanthosis, skin tags)</td>
<td>Gonadotropins (high LH or LH:FSH ratio &gt;2-2.5)*</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>General exam</td>
<td>Prolactin, Thyroid (TSH)</td>
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<tr>
<td></td>
<td></td>
<td>Androgens (Free and Total T**, DHEA-s)</td>
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<tr>
<td></td>
<td></td>
<td>Adrenal steroids (excess cortisol, 17-OHP)</td>
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<tr>
<td>Obesity (onset, progression)</td>
<td>May require pelvic exam (GYN)</td>
<td>Glycemic evaluation: fasting glucose, Hemoglobin A1c, c-peptide/insulin level, 2 hr glucose tolerance</td>
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<tr>
<td>Androgen related symptoms</td>
<td>Lipids (low HDL, high trigs, high LDL)</td>
<td>Hepatic function (fatty liver)</td>
</tr>
<tr>
<td>(acne, hirsutism, virilization)</td>
<td></td>
<td>Renal function (for treatment)</td>
</tr>
<tr>
<td>Family history</td>
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</tr>
</tbody>
</table>

*Only present in 1/3 of PCOS women
**Assay quality is important. Ensure using female reference range.

Pathology

- The pathogenesis of PCOS is not fully understood.
- There is evidence of a polygenic component.
- Likely genetic and environmental contributions.
- Hyperandrogenism & Insulin resistance are important elements in the development of PCOS but there are complex interactions involving many systems.
Pathology – Possible explanations

- HPG axis abnormality with GnRH dysregulation resulting in increased LH levels and exaggerated ovarian androgen production.
- Unmeasured enzymatic defect (ovarian +/- adrenal) favoring androgen excess.
- Insulin resistance as the culprit for both the metabolic and androgen (reproductive) abnormalities vs. vice versa?

Obesity, Insulin changes & PCOS

- Abdominal obesity promotes insulin resistance (IR) and compensatory hyperinsulinemia (HI).
- Increased visceral adipose mass increases free fatty acids which in turn affects insulin secretion and metabolism in the periphery.
- Insulin resistance has been described in both obese and normal weight PCOS women.
- Obesity appears to amplify the IR and HI in PCOS.
- Exposure to androgens can increase visceral fat in obese and normal weight PCOS women.


PCOS & Obesity

- Obesity is present in at least 50% of PCOS women.
- Obesity is thought to exacerbate PCOS.
- History of weight gain typically precedes the symptoms of PCOS.
- Links between androgen excess, insulin resistance and adipose tissue are being explored.
Metabolic consequences of PCOS

- Metabolic syndrome + reproductive abnormalities

- Intrauterine growth restriction
- Premature adrenarche
- Insulin resistance/obesity
- Ovulatory dysfunction, infertility, hirsutism, acne
- IR, obesity, IGT, T2DM, dyslipidemia
- Endometrial hyperplasia → cancer

Insulin resistance in PCOS

- Peripheral insulin sensitivity reduced in all PCOS women.
  - Insulin mediated glucose disposal is decreased by 35-40% in PCOS (compared to same weight controls).
  - Defect is worsened by obesity.
- Hepatic insulin resistance is demonstrated in obese women with PCOS.
Insulin resistance in PCOS

- Insulin compensation to insulin resistance and glucose levels are inappropriately low.
- "Disposition Index" Normally changes in insulin sensitivity are compensated by appropriate changes in insulin secretion = normal glucose tolerance.
- In PCOS (obese and non-obese) the disposition index is lower compared to weight matched controls.
- This perturbation is made worse with weight gain.


Insulin resistance in PCOS

- PCOS adipocytes may have a post-binding defect in insulin receptor-mediated signal transduction.
- Similar suggestion for skeletal muscle, the major site of insulin-mediated glucose uptake.

Adipocytes in PCOS

- Visceral adipocytes appear to have increased responsiveness to catecholamine stimulated lipolysis independent of obesity.
- The increase in visceral fat lipolysis leads to an increase in FFA release directly into the portal circulation.
- Portal FFA levels are major positive modulators of hepatic glucose production.
- Another mechanism for the increased risk for glucose intolerance in PCOS.

Adipocytes in PCOS – Role of Androgens

- Androgens inhibit adipocyte differentiation thereby increasing lipolysis & lipogenesis
- Testosterone induces IR in adipose tissue
- Insulin stimulates GnRH → ↑pituitary gonadotropins → ↑ovarian androgen production
- Insulin reducing SHBG production → ↑free androgen concentration
Schematic representation of a link between obesity and PCOS via adipokines.


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PCOS hormonal disruption

- Leptin’s role
  - Signal of energy sufficiency
  - Proportional to adipose mass and increased in obesity.
- PCOS subjects had higher leptin levels.
- Adiponectin correlates with insulin sensitivity.
- HMW adiponectin was lower in PCOS regardless of weight

PCOS hormonal disruption

- Ghrelin’s role
  - food initiation and termination
- Obese have lower fasting ghrelin levels and post-meal suppression may be impaired.
  - Rises with weight loss.
- PCOS subjects had less ghrelin rise with weight loss.

Moran LJ. J Clin Endocrinol Metab. 2004 Jul; 89(7):3337-44.

PCOS hormonal disruption

- PCOS is characterized by abnormalities in GnRH pulsatility (more LH action vs FSH).
  - Independent of obesity
  - Obese reproductively normal women do not have abnormalities in 24-hour LH and FSH plasma concentrations.

Androgen excess

- Androgen formation in the ovary and adrenal gland is dependent on P450c17 enzyme.
- Hyperactivity of the P450c17 enzyme is thought a key mechanism resulting in hyperandrogenism in PCOS.
Insulin receptor has been found to be abnormally phosphorylated resulting in inhibition of its action = insulin resistance.

P450c17 enzyme has been found to abnormally phosphorylated resulting in increased androgen biosynthesis = hyperandrogenemia.

Block of MEK/ERK pathways that help reduce androgenesis resulting from insulin stimulation.

Does obesity cause PCOS?

- Reproductive disturbances more common in obese women regardless of the diagnosis of PCOS.
  - Risk of anovulatory infertility increases at a BMI > 24 kg/m² or higher.
  - Weight reduction can restore regular menstrual cycles in these women.
- Yet, the majority of obese women do not develop hyperandrogenemia and do not have PCOS.
  - Non PCOS obese may have increased androgen production (esp w/upper-body obesity) but clearance is also increased = no net change
  - PCOS bioavailable androgen levels are increased.

Obesity → Androgens

- Obesity amplifies hyperandrogenism.
- Increased adiposity in women results in altered sex steroid balance.
  - Increased androgen production
  - Reduced SHBG
  - More estrogen available (less SHBG)
- Possible alterations in the HPA axis
  - Exaggerated ACTH response to CRH?
  - Altered ACTH pulsatile dynamics?
- Dietary contributors
  - High lipid load → decrease SHBG, increase free androgens

Does PCOS cause obesity?

- Androgens role in body composition.
  - Android: greater distribution of fat in the upper body
  - Gynoid: accumulating fat in the lower body.
- Most critical appears to be the presence of central/visceral adiposity.

Androgens → Insulin Resistance

- Androgens may induce an insulin resistance state
  - Activation of lipolytic cascade → increased FFA from visceral adipose depot.
  - Testosterone may impact muscle insulin sensitivity.
- Trials with anti-androgens (flutamidine and spironolactone) led to improvement in insulin resistance.

Androgens → Insulin Resistance

- Chronic exposure higher androgen concentrations may modify body fat distribution.
  - Rats exposed to high dose testosterone early in life lead to IR and accumulation of visceral adipose in adulthood.
  - Androgen treatment in nonobese female to male transexuals increased visceral fat and reduced insulin sensitivity.
  - Postmenopausal women exposed to androgens increased visceral fat independent of weight.
- PCOS abdominal tissue revealed larger-sized adipose cells in both obese and nonobese women
- Preferential abdominal accumulation of adipose tissue?

Androgens excess


Hyperinsulinemia and hyperandrogenism

- Insulin stimulates ovarian & adrenal androgen secretion.
- Insulin decreases SHBG synthesis in the liver which increases free androgen tissue availability.
- Insulin decreases IGFBP-1 in liver and ovary.
- Insulin upregulates ovarian IGF receptors resulting in amplification of IGF actions in the ovary.
- Insulin increases LH receptors in the ovary & sensitizes LH secreting pituitary cells to GnRH stimulation.
- Insulin promotes ovarian growth and cysts formations.


PCOS Management

- Weight loss improves hormone imbalance through improved insulin levels/sensitivity.
  - Decreased P450c17 enzyme activity, reduced leptin.
  - Reduced androgens, increased SHBG, improved ovulation/fertility → unique finding in PCOS women.
- Insulin lowering drugs reduced androgen concentration and improve SHBG levels.
  - Results were positive even without changes in weight.
  - Some data to suggest that obese PCOS women have favorable weight loss.
- Antiandrogens improve IR/HI in all PCOS women.
- OCPs reduce androgen activity and may improve weight/insulin sensitivity in some.


Summary

- Most experts agree that androgen excess is critical in describing PCOS.
- Evidence suggests that androgen excess may be causally involved in abdominal fat accumulation in women.
- In PCOS, those with more HA are described to have more metabolic dysfunction and CV risks.
- Correction of HA may improve the abdominal adiposity and related metabolic disorders. This treatment would still require TLC.
- Obese PCOS women appear to have more severe IR/HI as compared to weight matched controls.
Summary

- Increased androgen secretion by ovarian theca cells appears to be key in PCOS.
- Androgen excess favors the development of abdominal adiposity, insulin resistance, compensatory hyperinsulinism and subsequently further androgen excess.
- This cycles predisposes these women to metabolic dysfunction and CV risk.
- Increased androgens explain cutaneous manifestations of PCOS, intraovarian androgen excess leads to ovulatory dysfunction and polycystic ovarian morphology.
- In mild androgen excess, PCOS may only become apparent when associated with increased obesity or IR.
- Current therapies focus on addressing the androgen excess, IR and adiposity.

Proposed PCOS/Obesity Cycle

- Androgens contribute to IR/HI &Obesity
- Obesity and insulin dysregulation contribute to HA.
Thank you.