POLYCYSTIC OVARIAN SYNDROME

Presence of oligo- or anovulation in combination with hyperandrogenism.

- Chronic anovulation may present as irregular menstrual periods or amenorrhea.
- It is not essential to document anovulation by ultrasonography or progesterone measurements in the presence of a clear clinical history
- PCOS occurs in 85 to 90% of women with oligomenorrhea and in 30-40% of women with amenorrhea
- Diagnosed either by clinical (hirsutism) or laboratory (elevated testosterone or androstenedione)
- Should not be diagnosed if evidence of other causes of oligo-ovulation and hyperandrogenism(ovarian androgen secreting tumor or nonclassical adrenal hyperplasia)
- Prevalence of PCOS is approximately 5–7% of women of reproductive age
- 50% of PCOS women are obese and tend to have an android pattern of obesity

Elevated levels of serum LH - increased LH pulse amplitude and LH pulse frequency

- Steady-state levels of gonadotropins and ovarian steroids
    - “chronic estrous state”
    - Proliferation and hyperplasia of the endometrium
    - Can lead to unpredictable bleeding episodes
    - Unopposed estrogen exposure -confirmed by progesterone withdrawal test

- Women with PCOS have higher mean concentrations of LH
    - Increased bioactivity of LH
    - Low to low-normal levels of follicle stimulating hormone

- Obese PCOS women do not have elevated LH levels
    - normal LH level or normal LH/FSH ratio does not rule out PCOS
    - LH/FSH ratio is now not included in the diagnostic criteria of PCOS

- In research studies almost all women with PCOS have elevated LH secretion.
- In clinical practice - difficult to use a single measurement of LH to diagnose PCOS,
    - LH is secreted in a pulsatile manner
    - Normal range of serum LH concentration decreases with increasing body mass index (BMI)

Association between hyperinsulinemia and PCOS

- First noted by 1980

- Significant positive correlation between insulin, androstenedione and testosterone levels among PCOS women

- It is estimated that 20-40% of PCOS women have impaired glucose tolerance
    - Seven-fold higher than the rates in age and weight-matched women
    - Prevalence of type 2 diabetes mellitus is also increased in PCOS women (15% versus 2.3% in normal women)
    - Lean PCOS women have lower rates of carbohydrate intolerance
    - Lean PCOS women still have higher rates than age and weight-matched controls. PCOS is associated with insulin resistance independent of total or fat-free body mass
    - Obese PCOS women are more insulin resistant than obese non-PCOS or non-obese PCOS women

- Pancreatic beta cell secretory dysfunction in a subset of PCOS women
    - Probably has the highest risk of developing carbohydrate intolerance
    - Type 2 diabetes.
    - Oral glucose tolerance tests recommended for obese PCOS patients

- PCOS in 8 out 30 premenopausal women with type 2 diabetes
    - Insulin resistance is characterized by post-receptor defect in the action of insulin
    - Cause of this defect is still being elucidated

Action of insulin

- Binds to the cell-surface receptor
- Receptor undergoes auto-phosphorylation on specific tyrosine residues
- Accomplished by activation of insulin receptor tyrosine kinase
- Activated receptor then activates insulin receptor substrates (IRS-1,2 and 3)
- Binds to signaling molecules such as PI3 kinase
- Activates downstream signaling
- Leads to insulin-mediated glucose transport

PCO insulin resistance

- Abnormalities in both insulin receptor tyrosine kinase
- Mediators distal to the receptor are present in insulin resistance states
- Adipocytes from women with PCOS
- Adipocyte insensitivity to inhibition of lipolysis by insulin
- Decrease in maximal rates of adipocyte glucose uptake
- Occur in PCOS in the absence of obesity
- Decreased insulin receptor auto-phosphorylation in 50% of fibroblasts removed from PCOS women
- Due to increased receptor serine phosphorylation
- Serine phosphorylation - associated with decreased insulin receptor tyrosine auto-phosphorylation

- In vitro human theca cell studies
  - Insulin has direct stimulatory effects on ovarian steroidogenesis
  - Insulin produced a greater increase in androgen production by theca cells in PCOS than in cells obtained without PCOS
  - Effect is mediated specifically through insulin receptor
  - Insulin enhances the effect of LH on preovulatory ovarian follicles
  - Premature activation and subsequent follicle arrest
  - hyperinsulinemia (due to insulin resistance) drives the LH effect on ovarian theca cells
    - Causes androgen excess which are intrinsically programmed to produce more androgen
    - Excess androgens are known to interfere with the process of follicular maturation
    - Inhibiting ovulation
    - Producing more arrested follicles

- 1983 it was proposed that severe hyperinsulinemia caused by insulin resistance results in ovarian hyperandrogenism (Barbieri & Ryan)
- PCOS is associated with insulin resistance independent of total or fat free body mass
  - Hyperandrogenism, insulin resistance and acanthosis nigricans syndrome

- Cause of the insulin resistance – germ line mutation in the insulin receptor gene
  - Prevents normal function of the insulin receptor.

- Puberty: LH secretion rises
  - Severe insulin resistance
  - LH stimulation → hypersecretion of testosterone by the ovary
  - Often present with severe insulin resistance and hyperandrogenism including virilization and amenorrhea

- Acanthosis nigricans
  - Dermatologic manifestation of the hyperinsulinemia
  - Hyperandrogenism

- Clinical criteria suggestive of insulin resistance
  - BMI greater than 27 kg/m2
  - Waist-to-hip ratio greater than 0.85
  - Presence of acanthosis nigricans

- Laboratory criteria
  - Elevated fasting insulin concentration
  - Elevated glucose-to-insulin ratio

- Must have 2 of the following 3 manifestations
  - Irregular or absent ovulation
  - Elevated levels of androgenic hormones
  - Enlarged ovaries containing at least 12 follicles each

- Polycystic ovaries are defined - on ultrasound
  - To contain 12 or more follicles
  - Measuring 2 to 9 mm in diameter
  - Increased volume of 10 mL or greater
  - Only one ovary fulfilling these criteria is enough

- Polycystic ovaries are not necessary feature of PCOS
  - Many women with polycystic ovaries do not have PCOS
  - Should not be considered to have PCOS unless there is corroborating clinical evidence of the syndrome.

- Treatment of insulin resistance
  - Can reduce ovarian androgen secretion and
  - Cause the resumption of ovulatory menses.
  - Cause–effect relationship between insulin resistance and hyperandrogenism–anovulation.

- Typical Presentation
  - Chief compliant of hirsutism
  - Irregular menses
  - Infertility

- Treatment of Hirsutism
  - Combination of an estrogen–progestin contraceptive
  - Antiandrogen (spironolactone)

- Standard treatment for infertility
    - Clomiphene citrate and weight loss

Treatment with insulin sensitizers, metformin (biguanide which reduces plasma glucose concentrations in type 2 diabetes) and thiazolidinediones (Troglitazone and Rosiglitazone), improve both metabolic and hormonal patterns and also improve ovulation in PCOS

- Metformin
    - Does not lead to weight gain
    - Can induce weight loss
    - Predominantly works by reducing hepatic glucose production
    - Inhibiting gluconeogenesis both directly and indirectly (by decreasing free fatty acid concentrations)
    - May slightly improve peripheral insulin sensitivity in PCOS
    - Reductions in androgen levels
    - Improvements in ovulation
    - Reduce the high rates of gestational diabetes in PCOS

- Thiazolidinediones (TZDs)
    - Decrease peripheral insulin resistance
    - Enhancing insulin action
        - Skeletal muscle
        - Liver
        - Adipose tissue

Mechanism of action
- Binding and modulating the activity of a family of nuclear transcription factors
    - Peroxisome proliferator-activated receptors (PPARS)

- Shown an improvement of the androgen levels
    - Ovulation rate
    - Enhanced insulin sensitivity
    - No reduction in the weight of subjects
    - Decrease testosterone, androstenedione, DHEA
    - Increase in SHBG
        - Thereby causing a decrease in free testosterone levels
        - Improvement in insulin sensitivity
    - Improved both spontaneous and clomiphene-induced ovulation rates
    - Independent effects on ovarian steroidogenesis
    - Direct effect of TZD apart from improvement of insulin resistance ?

- PCOS women have higher circulating levels of inflammatory mediators
  - C-reactive protein
  - Tumor necrosis factor
  - Tissue plasminogen activator
  - Plasminogen activator inhibitor-1 (PAI-1)

- Hirsutism occurs in approximately 80% of PCOS women
- Documented by measuring androgen levels in the blood
  - Free testosterone
  - Total testosterone
  - Androstenedione
  - Dehydroepiandrosterone (DHEA)

- In obese PCOS women
  - Sex hormone binding globulin (SHBG) levels are decreased
  - Leads to an increase in free testosterone levels
  - Insulin is a negative regulator of the production of SHBG by the liver
  - SHBG levels are decreased in hyperinsulinemic conditions
  - Concentrations of sulfated DHEA (DHEAS) are also increased
    - Secreted exclusively by the adrenal glands
    - Mechanism of increased DHEAS production by the adrenals unknown
      - Insulin ?
      - IGF-1 ?

- Under influence of low but constant levels of FSH
  - Multiple follicles of the ovary are stimulated
  - Do not achieve maturation
  - Lifespan of the follicles may extend over several months
  - Leading to multiple follicular cysts
  - Luteinized in response to constant and relatively high LH levels
  - “arrested” follicles provide a constant supply of steroids
  - Atretic follicle becomes an androgenic follicle
  - Atretic follicles are deficient in aromatase activity

- Follicular cells from the small follicles of polycystic ovaries
  - Produce small amounts of estradiol
  - Show a dramatic increase in estrogen production when stimulated by FSH or IGF-1
  - FSH therapy induces a larger cohort of follicles to develop in women with PCOS
  - deficient in vivo ovarian response to FSH
  - Due to impaired interaction between signaling pathways associated with FSH and IGF1 ?

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References:
Dhindsa G, Bhatia R, Dhindsa M, Bhatia V. Insulin resistance, insulin sensitization and inflammation in polycystic ovarian syndrome. J Postgrad Med 2004;50:140-144 **** Excellent review of topic of PCO – most of above abstracted from this paper ******

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Vol. 101, No. 4, April 2003 ***** Excellent review of use of Metformin *****

FUNDAMENTAL QUESTIONS

1. Describe the PCO syndrome.
2. Describe the relationship of PCO with carbohydrate metabolism.
3. What is metformin? What benefit does it confer when given to women with PCO?
4. Where are androgens produced in the ovary?
5. What are some clinical problems associated with PCO?
6. What happens under the influence of sustained low levels of FSH?
7. Name some inflammatory mediators?
8. What is the role of obesity in PCO?
9. What happens to SHBG in obese women with PCO?
10. What is acanthosis nigricans?
11. Is hirsuitism common in PCO?