

POLYCYSTIC OVARY SYNDROME

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GENERAL CONSIDERATIONS

- Polycystic ovary syndrome (PCOS) is a syndrome of infertility, hyperandrogenism, hirsutism, obesity (not required) and amenorrhea or oligomenorrhea
- Transmitted as an autosomal dominant or x-linked trait
- Originally described by Stein and Levanthal as characterized by enlarged ovaries but enlarged ovaries need not be present
- The ovaries are often white and sclerotic, with a thickened capsule, multiple follicular cysts, hyperplastic theca and stroma.
- The diagnosis is a clinical one based on coexistence of chronic anovulation and varying degrees of androgen excess.

CLINICAL FINDINGS IN PCOS

- Obesity is usually present but may be absent, especially in young women
- H/o irregular periods usually from menarche followed by oligomenorrhea
- Increased body hair but only rarely true virilization
- Enlarged ovaries by transvaginal ultrasound but some patients have normal sized ovaries and 20% of normal women have cystic ovaries
- Spontaneous uterine bleeding occurs but may be unpredictable in time of onset, duration, and amount; occasionally the bleeding can be severe

ENDOCRINE FINDINGS IN PCOS

- Variable!
- In general, FSH and estradiol levels are at least as high as normal midfollicular levels but do not cycle normally

- PCOS patients usually bleed in response to progestin challenge but as there is no LH surge, there is no ovulation
- LH is high-normal often with an LH : FSH > 2
- Testosterone, androstenedione and estrone (the estrogen produced directly from androstenedione) tend to be elevated. Often only unbound (“free”) testosterone is elevated
- Androgen levels and physical signs do not correlate well

PATHOPHYSIOLOGY

- 4 factors are present:
 - anovulation
 - elevated but not surging LH
 - increased androgen production
 - follicular atresia without maturation
- 4 pathophysiologic abnormalities have been identified:
 - increased frequency of GnRH pulses
 - dysregulation of androgen secretion in the ovaries and sometimes in the adrenal glands
 - cystic changes in the ovaries
 - hyperinsulinism with insulin or a related peptide contributing to excess androgen production
- The precise relationship between hyperinsulinism and hyperandrogenism is not clear, but it is likely that high levels of insulin, acting through the insulin receptor, cause or aggravate androgen overproduction in ovaries
- Diabetes mellitus is uncommon but obese pts with PCOS usually have markedly elevated insulin levels and often manifest intolerance to glucose challenge.
- A fasting glucose-insulin ratio of < 4.5 can be used in non-Hispanic white women.

DIFFERENTIAL DIAGNOSIS OF PCOS

- Difficult! Many overlapping syndromes and closely related disorders
 - Hyperthecosis is a closely related disorder but here clinical androgen excess tends to be greater and frank virilism is often seen. Adrenal cortical excess is often present
 - Ovarian tumors can produce all the features of PCOS but here, the onset is usually more abrupt and there is clearer progression; for example previously normal women undergo a change in menses and increased hair growth with an ovarian tumor whereas PCOS manifests itself from menarche. In all ovarian tumors, the plasma testosterone level is > 200 ng/ml. A CT or MRI of the ovaries and adrenals is warranted.

HYPERINSULINEMIA AND INSULIN RESISTANCE IN PCOS

- Insulin resistance and its accompanying compensatory hyperinsulinemia are intrinsic features of PCOS. Diabetes is uncommon however.
- It is unlikely that hyperandrogenism causes insulin resistance in PCOS as insulin resistance persists in women in whom both ovaries have been removed surgically. Likewise, insulin resistance persists in PCOS women who have androgen production suppressed by long-acting gonadotropin hormone-releasing hormone agonists.
- It is more likely that hyperinsulinemia causes hyperandrogenism in PCOS women in the following ways:
 - An inherent ovarian defect probably exists in PCOS women which makes the ovary either susceptible to or more sensitive to insulin stimulation
 - Insulin stimulates ovarian androgen production
 - Insulin directly and independently reduces serum sex hormone-binding globulin (SHBG) levels
 - The net result of these actions is an increase in free testosterone levels
- Medications which reduce circulating insulin (e.g. metformin) have proven effective therapies in PCOS, reducing circulating androgens
- Medications which inhibit insulin release (diazoxide and octreotide) induce marked glucose intolerance in PCOS patients.
- Medications which improve insulin sensitivity (metformin and troglitazone) do not induce glucose intolerance in PCOS patients.

TREATMENT OF PCOS

- Multiple approaches are possible depending upon the needs of the pt:
 1. Decrease ovarian androgen production
 - Wedge resection of the ovary: standard therapy in the past but no longer popular because the anovulatory state often returns within a few months of the procedure
 - Oral contraceptives
 2. Decrease peripheral estrogen formation which will decrease acyclic positive feedback on LH secretion and negative feedback on FSH secretion
 - Weight reduction

3. Increase FSH production
 - Clomiphene : standard therapy when fertility is desired but often produces multiple ovulation
 - Human menopausal gonadotropin (hMG)
 - LHRH (gonadorelin) by portable infusion pump
 - Purified FSH (urofollitropin)
 4. Decrease circulating androgens by decreasing circulating insulin
 - Improve insulin sensitivity through use of metformin or troglitazone
- Choice of therapy depends on clinical findings and needs of the patient
 - If the woman is not hirsute and does not desire pregnancy, cyclic withdrawal menses may be induced by administering medroxyprogesterone acetate 10 days per month. This prevents the development of endometrial hyperplasia
 - If the woman is hirsute and does not desire pregnancy, androgen production may be suppressed with oral contraceptives
 - Dysfunctional uterine bleeding may be controlled with oral contraceptives
 - If pregnancy is desired, ovulation must be induced. Drugs include clomiphene (works 75% of the time) metformin or hMG or urolitropin or gonadorelin.

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