**PCOS and hyperprolactinemia**

* **PCOS** Overview :
  + PCOS is a complex endocrine disorder affecting women of childbearing age characterized by increased androgen production and ovulatory dysfunction .
  + Prevalence 6-8% of normal population
  + Leading cause of anovulatory infertility 40% of cases , and hirsutism
  + Women with PCOS have an increased risk of miscarriage, insulin resistance, hyperlipidemia, type 2 diabetes . high levels of estrogen may cause >> cardiovascular disease, and endometrial cancer
  + PCOS was first identified by Stein and Leventhal in 1935 ,They described a group of women who were obese and infertile, with enlarged ovaries with multiple cysts .
* **Pathogenesis :**
  + Insulin resistance → hyperinsulinemia → theca cell proliferation (produces testosterone) → hyperandrogenism → PCOS .
* **Genetic link :**
  + Familial clustering of PCOS common .
  + 1st degree relatives of patients with PCOS may be at high risk for diabetes and glucose intolerance .
  + Mothers and sisters of PCOS patients have higher androgen levels than control subjects .
* **Diagnostic criteria :**
  + NIH Criteria :
    - Menstrual irregularity due to anovulation or oligo-ovulation (oligomenorrhea or amenorrhea )
    - Evidence of clinical or biochemical hyperandrogenism
      * Hirsutism, acne, male pattern baldness
      * High serum androgen levels
    - Exclusion of other causes (CAH, tumors, hyperprolactinemia)
  + Rotterdam Criteria (2 out of 3) :
    - Menstrual irregularity due to anovulation oligo-ovulation
    - Evidence of clinical or biochemical hyperandrogenism
    - Polycystic ovaries by US :
      * presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume
    - In addition, other etiologies (congenital adrenal hyperplasias, androgen-secreting tumors, Cushing's syndrome) must be excluded.
  + AES criteria : (presence of three features )
    - androgen excess (clinical and/or biochemical hyperandrogenism)
    - ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology)
    - exclusion of other androgen excess or ovulatory disorders
* **hyperandrogenism :**
  + Hirsutism, acne, male pattern balding, alopecia
  + 50-90% patients have elevated serum androgen levels
  + Free testosterone levels “most sensitive”
  + Rare: increased muscle mass, deepening voice, clitormegaly (should prompt search for underlying neoplasm)
* **Hirsutism :**
  + Is the presence of terminal hair in a female body in a male-type pattern, includes hair on 9 body areas: upper lip, chin, chest, upper back, lower back, upper and lower abdomen, upper arm and thigh
  + Method to determine presence of hirsutism uses a visual score, most common is” modified Ferriman-Gallwey “ score
  + 0 score represents absence of terminal hair and score of 4 represents extensive terminal hair growth. Hirsutism is defined by an mGF score of ≥ 6
  + However, prevalence of hirsutism varies according to race and ethnicity of population
* **Acne and androgenic alopecia :**
  + Acne affects 15-25% PCOS patients but unclear whether its prevalence is significantly increased in these patients over general population.
  + Androgenic alopecia or scalp hair loss may affect 5 – 50% PCOS patients but further studies are needed to better define this prevalence .
* **Ovarian abnormalities : (on US )**
  + Thickened sclerotic cortex
  + 10-12 subcapsular follicles 2-9 mm (necklace-shape )
  + 80% of women with PCOS have classic cysts (maybe absent in PCOS)
* **Infertility :**
  + Due to Intermittent ovulation or anovulation
  + Inherent ovarian disorder—studies show reduced rated of conception despite therapy with clomid
* **Obesity :**
  + Prevalence of obesity varies from 30-75%
  + 2/3 of patients with PCOS who are not obese (MBI <25) have excessive body fat and central adiposity
  + Obese patients can be hirsute and/or have menstrual irregularities without having PCOS
  + ½ patients with PCOS are obese
  + > 80% are hyperinsulinemic and have insulin resistance (independent of obesity)
  + Hyperinsulinemia contributes to hyperandrogenism through production in the theca cell and through its suppressive effects on sex hormone binding globulin production by the liver
* **Acanthosis Nigricans :**
  + Velvety plaques on nape of neck and intertriginous areas
  + Epidermal hyperkeratosis
  + Associated with insulin resistance
* **Differential diagnosis of PCOS :**
  + Hyperprolactinemia
  + Congenital Adrenal Hyperplasia
  + Ovarian and adrenal tumors
  + Cushing’s syndrome
  + Drugs: danazol; OCPs with high androgenicity
* **Investigations and findings :**
  + Serum HCG (to exclude pregnancy because it’s the most common cause of amenorrhea in reproductive age )
  + Serum prolactin
  + Thyroid function test
  + FSH: normal ,we should rule out ovarian failure (menopause > 15 IU-L )
  + Serum luteinizing hormone (LH)—elevated
  + Serum estradiol—normal “predominant estrogen in reproductive age group is estradiol”
  + Serum estrone—elevated “predominant estrogen in PCOS and menopause is estrone “
  + Fasting glucose: elevated
  + 2 hour OGTT: elevated
  + Fasting insulin: elevated
  + Free testosterone: elevated
  + DHEA-S: normal
  + 17-hydroxyprogesterone: normal
  + Pelvic US
  + Lipids (hyperlipidemia )
* **Treatment : (Depends on goal of treatment)**
  + Weight loss “very effective , 5-10 % of her weight “
  + Hirsutism :
    - Mechanical hair removal
    - Vaniqa cream (eflornithine hydrochloride)
    - OCPs with minimal androgenicity
    - OCP plus antiandrogen (spironolactone , Flutamide or Cypreterone acetate)
      * Spironolactone, 50-200 mg per day
  + Oral Contraceptives :
    - Suppress ovarian androgen
    - Increase SHBG (sex-hormone-binding-globulin ), which reduces free testosterone
    - Regular menstrual cyclicity
    - Progestin opposition
    - Contraception
  + Anti-androgens :
    - Spironolactone
      * Androgen receptor blockade, Steroid enzyme inhibition
      * Aldosterone antagonism, Lower blood pressure
      * Potassium sparing, Dose: 100-200 mg/day
    - Flutamide
      * Non-steroidal, selective anti-androgen
      * Liver function tests, Dose: 125-250 mg/day
    - Finasteride
    - Cypreterone acetate
  + Oligomenorrhea :
    - Combination estrogen-progestin pill first line when fertility is not desired
    - Decrease in LH secretion and decrease in androgen production
    - Increase in hepatic production of sex-hormone binding globulin
    - Decreased bioavailablity of testosterone
    - Decreased adrenal androgen secretion
    - Regular withdrawal bleeds
    - Prevention of endometrial hyperplasia
  + insulin-sensitizing agents : (Metformin )
    - will restore ovulation and menses in > 50% of patients
    - Treat with cyclic progestin to reduce endometrial hyperplasia if regular menses not attained
    - 10 mg for 7 to 10 days every two to four months
    - Decreases hepatic glucose production
    - Reduces need for insulin secretion
    - Improves insulin sensitivity (increases peripheral glucose uptake and utilization)
    - Antilipolytic effect—reduces fatty acid concentrations and reduces gluconeogenesis
    - Side effects : GI upset >> Diarrhea, nausea, vomiting, flatulence, indigestion, abdominal discomfort Caused by lactic acid in the bowel wall Minimized by slow increase in dosage
    - Lactic acidosis—rare
* **Women with anovulatory infertility who want to get pregnant :**
  + Weight Reduction :
    - 50% treatment of PCOS is simply – weight control.
    - Even if one loses 5-10 kg - the effect is tremendous
  + Clomifene Citrate (to induce ovulation , do not continue treatment for longer than 6 months ) or Metformin or A combination .
  + If patient is resistant to Clomifene Citrate :
    - Laparoscopic Ovarian drilling (one ovary , 4 holes , for 4 seconds , not more than 4 mm in depth in cortex) side effects : Pereovarian adhesions and Premature ovarian failure-very rare .
    - Combined treatment with clomifene citrate and metformin if not already offered as fist – line treatment or
    - Gonadotrophines (injectable ovulation induction agent )
* **Complications of PCOS :**
  1. Insulin Resistance :
     + 10% have Type 2 Diabetes
     + 30%-35% have Impaired Glucose Tolerance (IGT)
  2. Obesity
     + 50% of PCOD patients are obese
     + Amplifies biochemical and clinical abnormalities of PCOS
  3. Endometrial Cancer :PCOS women found an increased risk of endometrial cancer
  4. Cardiovascular Disease: Increased risk of myocardial infarction in
  5. Sleep Apnea
  6. Dyslipidaemia
  7. Hypertension and Endothelial Dysfunction
  8. Depression :Higher prevalence in PCOS patients, associated with higher body mass index
* **Pregnancy Complications of PCOS :**
  1. Spontaneous miscarriage (due to high LH)
     + Increased in high BMI/PCOS patients
  2. Impaired Glucose Tolerance
  3. Gestational Diabetes
  4. Hypertension
  5. Small for Gestational Age
* **Hyperprolactinemia** overview **:**
  + Hyperprolactinemia is a condition of elevated serum prolactin. Which is an amino acid protein produced in the anterior pituitary gland.
  + Its primary function is to enhance breast development during pregnancy and to induce lactation.
  + Secretion is pulsatile; it increases with sleep, stress, pregnancy, and chest wall stimulation or trauma, and therefore must be drawn after fasting. Normal fasting values are generally less than 25-30 ng/mL,
  + Dopamine has the dominant influence over prolactin secretion. Secretion of prolactin is under tonic inhibitory control by dopamine.
  + This condition occurs in less than 1% of the general population and in 5-14% of patients presenting with secondary amenorrhea (high prolactin will suppress FSH release which leads to amenorrhea ).
  + Approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Of these patients, approximately 30% have prolactin-secreting tumors.
* **Presentation :**
  + Oligomenorrhea ,amenorrhea, or infertility (results from prolactin suppression of gonadotropin-releasing hormone (GnRH).)
  + Galactorrhea ( due to the direct physiologic effect of prolactin on breast epithelial cells)
  + visual-field defects (in the case of prolactinomas which occurs in 1/3 of cases of hyperprolactinemia)
* **causes :**
  1. Primary Hypothyroidism (rare cause, high TSH )
  2. Idiopathic “most common”
  3. Drug: usually with prolactin levels of less than 100 ng/mL.
     1. Dopamine-receptor antagonists (eg, phenothiazines, butyrophenones, thioxanthenes, risperidone, metoclopramide, sulpiride, pimozide)
     2. Dopamine-depleting agents (eg, methyldopa, reserpine)
     3. Others (eg, isoniazid, danazol, tricyclic antidepressants, monoamine antihypertensives, verapamil, estrogens, antiandrogens, cyproheptadine, opiates, H2-blockers [cimetidine], cocaine)
  4. If no obvious cause is identified or if a tumor is suspected, MRI should be performed.
     + a prolactinoma is likely if the prolactin level is greater than 250 ng/mL and less likely if the level is less than 100 ng/mL. a level of 500 ng/mL or greater is diagnostic of a macroprolactinoma.
  5. Prolactin-secreting adenomas are divided into 2 groups:
     1. microadenomas (more common in premenopausal women), which are smaller than 10 mm and
     2. macroadenomas (more common in men and postmenopausal women), which are 10 mm or larger.
* **Investigations :**
  1. Pregnancy test as many women present with amenorrhea
  2. TSH
  3. Visual field studies
  4. MRI if prolactin level is high: MRI can detect adenomas that are as small as 3-5 mm
* **Treatment :**
  + Patients with hyperprolactinemia and no symptoms can be monitored without treatment
  + If the patient had hyperprolactinemia but symptomatic such as amenorrhoea, prescribe either:
    - Bromocriptine 2.5 mag once or twice daily with meals because it has severe side effects such as severe nausea and GIT bleeding, headache, hypotension, OR
    - Cabergoline 0.5 mg weekly. Follow up with prolactin level assessment every 2-3 months which had no serious side effect as bromocriptine.
  + If the woman had primary hypothyroidism: give thyroxine
  + If the cause is drugs, stop them if you can .
  + Hyperprolactinemia with or without micro or macro adenoma we should start treatment medically first (cabergoline or bromocriptine ), because even macroadenomas may respond to drugs , if no response go for surgery .
  + DEXA scanning every 6 months to exclude osteoporosis (low dose estrogen significantly improves the patient's quality of life)
  + CT scan or MRI every 6 months for follow up .
* **Surgical treatment of prolactinoma :**
  + indications :
    1. Patient drug intolerance,
    2. Tumors resistant to medical therapy (high prolactin levels after 3 months of medical therapy , or CT not improved)
    3. Patients who have persistent visual-field defects in spite of medical treatment,
    4. Patients with large cystic or hemorrhagic tumors.
    5. Transspenoidal surgery “ best treatment” In patients with symptomatic prolactinomas who are either not responding to high doses of dopamine agonists or cannot tolerate the high doses.
* **Notes :**
  + predominant estrogen in pregnancy is estriol “fetal in origin” .
  + prolactin starts to elevate at 3rd month of pregnancy , and stays elevated during period of breastfeeding .

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