**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 .

done by : Noor Daher Al-hijjaj ☺

check pictures in the slide