र-वार-श्य विभाग की पहल



पॉलीसिस्टिक ओवरी डिसऑर्डर (PCOD) & पॉलीसिस्टिक ओवरी सिंड्रोम (PCOS)





STREAMING

यह कार्यक्रम स्वास्थ्य विभाग और राज्य स्वास्थ्य एवं परिवार कल्याण संस्थान (SIHFW), उत्तर प्रदेश की पहल पर उत्तर प्रदेश टेक्निकल सपोर्ट यूनिट (UPTSU) के सहयोग से हो रहा है।

Principal Secretary, Medical Health & Family Welfare, U.P. Shri Partha Sarthi Sen Sharma

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POLYCYSTIC OVARIAN DISEASE

Normal ovary

Polycystic ovary

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HISTORY

Originally described by Irving F. Stein and Michael I. Leventhal in 1935, first known as the *"Stein-Leventhal syndrome"*

The characteristic polycystic ovaries develop when chronic inflammatory state persists for a sufficient length of time.

The polycystic ovaries result from functional derangement, not from specific central or local defect.



DEFINITIONS AND EPIDEMIOLOGY

PCOD- Polycystic ovarian disease- multiple small **immature follicles arranged in periphery of the ovary**

PCOS- Polycystic ovarian syndrome- a syndrome with reproductive, metabolic and psychological features

- The polycystic ovarian disease and syndrome are most commonly seen in reproductive age group.
- The condition affects 8-13% of women worldwide.
- Prevalence in India is 3.7 to 22.5% out of which 9.3 to 36% in adolescents

PATIENTS PRESENT WITH DIVERSE CLINICAL FEATURES



EUGONADOTROPIC EUESTROGENIC ANOVULATORY CONDITION (WHO GROUP II)

Туре	Hormone profile	Incidence (among anovulatory females)	Conditions
Group I- HYPOGONADOTROPIC HYPOGONADISM ANOVULATION	Decreased FSH Decreased Estrogen	5-10%	Stress(physical,emotional or nutritional), weight loss, excessive exercise, anorexia nervosa, Kallman syndrome
Group II- NORMOGONADOTROPIC NORMOESTROGENIC ANOVULATION	Normal FSH Normal Estrogen Normal or Increased LH	75-85%	PCOS
Group III HYPERGONADOTROPIC ANOVULATION	Increased FSH	10-20%	Premature ovarian failure
HYPERPROLACTINEMIC ANOVULATIONDecreased FSH Decreased Estrogen Increased Prolactin		5-10%	Hypothalamic/pituitary disorders

PATHOPHYSIOLOGY-ENDOCRINE





PATHOPHYSIOLOGY-ENDOCRINE



preventing progressive follicular development



PATHOPHYSIOLOGY-METABOLIC

Insulin Resistance

- Insulin resistance is highly correlated with intra-abdominal obesity, because visceral fat is metabolically more active than subcutaneous fat.
- Sensitive to lipolysis, releases more free fatty acids, and produces a number of cytokines involved in insulin resistance,



DIAGNOSTIC CRITERIA-"Revised Rotterdam Criteria"



Menstrual irregularity due to anovulation or oligo-ovulation

In adults, 2 out of 3 criteria should be present



Evidence of clinical or biochemical hyperandrogenism



Polycystic ovaries by Ultrasonogarphy or elevated AMH In Adolescents - Both

hyperandrogenism and ovulatory dysfunction are required and ultrasound is not recommended to diagnosis.

IRREGULAR CYCLES AND OVULATORY DYSFUNCTION

- In the first year post menarche: considered normal as part of pubertal transition
- >1 to < 3 years post menarche: < 21 or > 45 days is abnormal
- **3 years post menarche to perimenopause:** <24 or >38 days or <8 cycles per year
- > 1 year post menarche: > 90 days for any one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)
- Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed, serum progesterone levels can be measured.

HYPERANDROGENISM- CLINICAL

- Acne and Alopecia
- The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.
- There are no universally accepted visual assessments for evaluating acne



HYPERANDROGENISM- CLINICAL

- HIRSUTISM Excessive growth of terminal hair with male pattern of distribution.
- Increased androgen production and skin sensitivity to androgens, depending on genetically determined local activity of 5<u>α</u> reductase.
- HYPERTRICHOSIS- androgen independent terminal hair in non sexual areas (such as trunk and extremities)
- VIRILIZATION- marked and global masculine transformation that includes coarsening of voice, increase in muscle mass, clitoromegaly (normal dimesion-3.4±1mm width by 5.1±1.4 mm length)

MODIFIED FERRIMAN GALLWEY SCORE





- Hirsutism is scored by Modified Ferriman-Gallwey system
 - Total score 36
 - <8- mild hirsutism</p>
 - 8-15- moderate hirsutism
 - >15- severe hirsutism

HYPER ANDROGENISM - BIOCHEMICAL

Calculate free testosterone free androgen index (best test)

FAI=100 x (Total testosterone/SHBG)

For women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.

 Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS.

ULTRASOUND AND POLYCYSTIC OVARIAN MORPHOLOGY

- The transvaginal ultrasound using transducers with a frequency bandwidth that includes 8MHz.
- Follicle number in adults >20 follicles in at least one ovary, or >10 in one section, or an ovarian volume ≥ 10cm3.
- Ensuring no corpora lutea, cysts or dominant follicles.
- For adolescents with gynaecological age <8 years(i.e. 8 years since menarche), USG is inadequate because peak ovarian maturity has not been reached yet.
 Hence, PCOD is not included in the diagnostic criteria



ULTRASOUND AND POLYCYSTIC OVARIAN MORPHOLOGY ESHRE 2018

- In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.
- Other ultrasound parameters for diagnosis of PCOS includes:-
 - ✓ ovarian area;
 - maximum number follicles in a single sonographic plane (FSSP);
 - ✓ peripheral distribution of ovarian follicles;
 - bright ovarian stroma



CONDITIONS THAT CAN MASQUERADE AS PCOS- EXCLUSION CRITERIA

Condition	Features shared with PCOS	Unique features and methods for exclusion
Late onset congenital adrenal hyperplasia	Oligoanovulation Hyperandrogenism Hyoperandrogenemia	Autosomal recessive disorder Elevated 17-OHP levels is the commonest variant due to 21- hydroxylase deficiency
Androgen secreting tumor Ovarian Adrenal	Oligoanovulation Hyperandrogenism Hyperandrogenemia	Signs of virilisation Markedly elevated total testosterone levels Elevated DHEA-S levels
Cushing syndrome	Oligoanovulation Hyperandrogenism Hyoperandrogenemia	Clinical stigmata-Hypertension, moon facies, buffalo hump, skin plethora Elevated 24 hr urinary free cortisol

CONDITIONS THAT CAN MASQUERADE AS PCOS- EXCLUSION CRITERIA

Condition	Features shared with PCOS	Unique features and methods for exclusion
Hyperplolactinemia	Oligoanovulation	Elevated prolactin levels
Hypothyroidism	Oligoanovulation Coarsing of hair Hair loss	Elevated TSH levels Positive Antithyroid antibodies(Hashimoto thyroiditis)
Androgenic agents Antidepressants Antiseizure	Oligoanovulation Hyperandrogenism	Androgen exposure-Supressed FSH/LH levels, Elevated testosterone Antidepressants and antiseizure- Hyperprolactinemia
Severe insulin resistance syndrome	Oligoanovulation Hyperandrogenism Hpyerandrogenemia	Elevated fasting insulin levels Acanthosis nigricans HAIR-AN syndrome

FOUR PCOS PHENOTYPES

Phenotype A	
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Androgen
 excess +
 ovulatory
 dysfunction
 + polycystic
 ovarian
 morphology

Phenotype B

 Androgen excess + ovulatory dysfunction

Phenotype C

 Androgen excess + polycystic ovarian morphology

Phenotype D

 Ovulatory dysfunction
 + polycystic
 ovarian
 morphology

ADOLESCENTS WITH PCOS

- Clinical or biochemical evidence of androgen excess is essential because other features of PCOS may be normal features of non-PCO adolescent girls.
- Clinical markers for adolescent PCOS- Obesity or BMI>25 and features of hyperandrogenism like hirsutism, acne, acanthosis nigricans and premature pubarche.
- Biochemical markers of adolescent PCOS- increased Fasting insulin/Fasting Glucose ratio (Normal<4.5), elevated free testosterone, DHEAS and 17-OHP
- LH/FSH ratio may be normal

A 19 year old obese female came to OPD with complains of irregular menses and excessive hair growth over face and lower abdomen since 4 months. How will you proceed?



Menstrual History-Menarche-13 years, cycle length-50 days, duration-8 days, flow-reduced, Dysmenorrhoea-Absent



Physical examination- BP=112/76 MMHG BMI=32 kg/m2 Waist circumference=96 cms Hirsutism-12 on mFMG Score Acne present, alopecia not present Acanthosis nigricans present over nape of neck



Laboratory tests	Values
Serum prolactin r/o hyperprolactinemia (pituitary tumor)	20-50 ng/ml- treat before PCOS
Thyroid function test r/o hypothyroidism (can cause oligo./ amenorrhea)	Treat before PCOS
LH:FSH ratio - reversal of ratio	>2-3 suggests PCOS
Fasting insulin	> 12 mIU/ml s/o insulin resistance
Insulin (2 hr post 75 gm glucose)	> 155 mIU/ml s/o insulin resistance
S.AMH Levels (produced by granulosa cells of follicles measuring less than 4 mm (preantral and antral follicles).	>5 ng/ml s/o PCOS

Laboratory tests	(Normal range)
Total testosterone	20-80 ng/ml
Free testosterone	0.6-6.8 pg/ml
DHEAS	100-350 mcg/dl
Free androgen index (T.testosterone /SHBGx100)	0.4-8.4
(17-OHP)	30-200 ng/dl
HDL	>50mg/dL
triglycerides	<150 mg/dl –

In this patient-

- S.TSH- 4.1 mIU/ml (N)
- S.Prolactin- 12 ng/ml (N)
- S.LH-18 mIU/ml
- S.FSH- 8.02 mIU/ml, (N)
- T. Testosterone: 100 ng/ml
- 17 hydroxyprogesterone-205 ng/ml
- Fasting insulin: 100 miu/ml
- BS Fasting-88 mg/dl(N) ,75 gm OGTT-122 mg/dl (N)
- S.Lipid Profile-Total Cholesterol-215 mg/dl, S.triglyceride-172 mg/dl,S.LDL-110 mg/dl,S.HDL=40 MG/DL

LH:FSH Ratio-2.2 :1



MANAGEMENT OF PCOS

Once diagnosed, assessment and management should address reproductive, metabolic, cardiovascular, dermatologic, sleep and psychological features. Hence treatment includes following components:

- Lifestyle management
- Counseling
- Pharmacological treatment OCPs, Antiandrogens, Insulin sensitisers, GnRH agonists
- Supplements- Vit D
- Surgical Ovarian drilling

COUNSELLING & LIFESTYLE MODIFICATION

- Weight reduction is the first line approach for overweight and obese women
 - Increases SHBG conc. reducing free androgens levels.
 - \succ Improves ovulatory function \Rightarrow increasing conception rates.
 - Achievable goal i.e. 5% to 10% reduction in weight within 6 months is considered successful.
 - To achieve weight loss, an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day) is effective.

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COUNSELLING & LIFESTYLE MODIFICATION

- Exercise interventions -Daily 10,000 steps is ideal, including activities of daily living.
- Self monitoring including fitness tracking devices and step counts could be used as a adjunct to minimise sedentary behaviours.
- Anti-obesity agents and bariatric/metabolic surgery may be considered based on general population guidelines, balancing potential for benefits and sideeffects
- Laser therapy is effective for hair reduction in some subgroups.



1. ORAL CONTRACEPTIVES

- Combined pills are recommended for management of clinical hyperandrogenism and/or irregular menstrual cycle.
- Low dose combined pills containing Ethinyl estradiol 20-30 ug + 3rd or 4th generation non androgenic progestogens (Desogestrel, Gestodene, Drosperinone) are mainstay in the treatment of PCOS.
- Preference for lower dose preparations and those with less side-effects
- Mechanism of Action: Estrogen raises SHBG levels and reduces free testosterone levels. Progestin component through negative feedback supresses LH secretions and thereby androgen production.

OCPS USED IN PCOS

Brand Name	Formulation	No. Of Tablets	Cost (INR)	Benefits
1.Yasmin	Drosperinone 3 mg+ EE 30 ug	21	300	Good for skin do not cause weight gain. Preferred
2.Dronis 20	Drosperinone 3 mg+ EE 20 ug	24	250	
3.Novelon	Desogestrel 0.15 mg+EE 30 ug	21	69	Lower the risk of endometrial hyperplasia and carcinoma, safe and effective contraception.
4.Femilon	Desogestrel 0.15 mg+EE 20 ug	21	75	
5.Minesse	Gestodene 60ug+EE 15 ug			







2. ANTIANDROGENS

Antiandrogens have a limited role for hirsutism and alopecia.

They are used where other therapies (cosmetic therapy and COCs) are ineffective or are contraindicated.

Best used in combination with OCPs.

- Side effects -undervirilisation of male fetus if patient conceives during treatment.
- Most common anti androgens used are spironolactone, cyproterone acetate, finasteride and flutamide

- ✓ **SPIRONOLACTONE** is an Aldosterone receptor antagonist with structural similarity to progestins and competes with DHT for binding to androgen receptor.
- \checkmark Also inhibits ovarian and adrenal and rogen production.
- √Dose- 50-100 mg/day twice daily for 6 months
- √Side effects: Diuresis, Hyerkalemia (Monitoring of potassium levels not necessary in women with normal renal function), abnormal bleeding.
- \checkmark Cost : Rs 60 for 15 tabs

CYPROTERONE ACETATE is a derivative of 17-OHP.

An Androgen receptor antagonist that inhibits enzymes involved in androgen synthesis.

- ✓ "Dianette" or "Diane 35" or "Krimson 35" are the lower estrogen dose formulation containing 35ug EE+2 mg CPA.
- ✓ Side effects- Fatigue, edema, weight gain, loss of libido and mastalgia
- √It should not be used as first line drug due to higher risk of venous thrombosis.



FINASTERIDE

FLUTAMIDE

- Inhibits 5@ reductase type 1, thus blocks the conversion of testosterone to more androgenic DHT
- Dose: 1mg daily
- Side effects: Under virilization of male fetus
- Cost: Rs266

- Non steroidal androgen receptor antagonist
- Primarily used in the t/t of prostate cancer.
- Dose: 250-750 mg daily inhibits hair growth velocity and is as effective as spironolactone
- Side effect: Severe hepatotoxicity
- Cost:Rs 80-90 for 10 tablets



3. INSULIN SENSITISING AGENTS

METFORMIN

- Oral Biguanide, currently the most widely used drug for Type 2 DM.
- Decreases hepatic glucose production, intestinal glucose uptake and increases peripheral insulin sensitivity
- Decreases weight, BMI, Blood pressure and LDL cholesterol.
- Dose :1500-2000 mg daily.
- Side effects: Diarrhoea, nausea, vomiting, flatulence, indigestion, abdominal discomfort, malabsorption of Vit B12, Lactic acidosis (rare)
 - Caused by lactic acid in the bowel wall
 - Minimized by slow increase in dosage

When to use Metformin in PCOS?

- Management of metabolic features- impaired fasting glucose, impaired glucose tolerance, abnormally elevated HbA1c levels or diabetes, central obesity, hypertension and dyslipidemia.
- BMI >=25 kg/m2
- In combination with COCP, where COCP and lifestyle management do not achieve desired goals.
- Contraindicated in liver, kidney and major cardiovascular disease

Metformin and Pregnancy

- No evidence of increased risk of fetal malformations.
- Reduces the risk for miscarriage as women with PCOS are at higher risk.
- Reduces the risk of developing gestational diabetes.
- However, for women who are on metformin it may be reasonable to consider continuing through the first trimester of pregnancy.

THIAZOLIDINEDIONES

MYOINOSITOL

- Used only when metformin is not tolerated and for metformin resistant cases.
- Drugs- Rosiglitazone, Pioglitazone
- Dose: 30 mg daily
- Side effect: Liver toxicity

- Increases glucose cell intake
- Increases oocyte quality
- Reduces amount of FSH used during IVF CYCLES
- Improves metabolic and hormonal parameters in PCOS
- Increases SHBG, estrogen and progesterone
- Dose: 2g twice daily

4. GnRH Agonists

- GnRH therapy is considered in women with severe HA who fails to respond to E+P combinations and Antiandrogens.
- Supression of LH dependent ovarian androgen production
- GnRH agonists- Leuprolide, Nafarelin, Goserelin.
- Side effects- Hypoestrogenism, Osteoporosis.
- "Add-back therapy": To eliminate estrogen deficiency symptoms and bone loss ,cyclical estrogen and progesterone or an OCP can be added when GnRH agonist is planned to be used for longer than 3 months.

5. VITAMIN D

- As per the Endocrine Society guidelines serum 25-hydroxyl level<25 ng/ml has been associated for reduced likelihood for ovulation and live birth.
- Judicious supplementation of vitamin D represent a simple, cost-effective and safe approach towards optimising fertility treatment –related success.
- 50,000 IU of Vit D2 weekly for 8 weeks f/b 50,000 IU once every other week to maintain sufficiency.

Psychological Care

- Depressive and anxiety symptoms are significantly increased and should be screened for in all women with PCOS, with psychological assessment and therapy as indicated.
- Greater awareness of psychological features including eating disorders and impacts on body image and quality of life is needed.
- Shared decision making and a self-empowerment are fundamental and integrated models of care should be developed, funded and evaluated

PCOS & INFERTILITY

- Chronic anovulation is one of the most common causes of infertility in PCOS patients.
- PCOS II trial established superiority of Letrozole over CC in achieving significantly higher ovulation rate, singleton pregnancy and Live birth rate (27.5 %vs 22%). Letrozole is the first line agent for ovulation induction in women with PCOS and those with CC resistance.
- Clomiphene alone or in combination with metformin, gonadotropins or ovarian surgery have a role as second-line therapy
- Women who fail to conceive despite multiple successful ovulations should be considered for IVF as third line therapy

CLOMIPHENE CITRATE

LETROZOLE

- SERM (Selective estrogen receptor modulator)
- Competitively binds the estrogen receptors at the level of the hypothalamus, releasing the negative feedback effect of estrogen and rise in endogenous FSH secretion
- Dose- 50mg OD (Max. 150mg)

- Aromatase inhibitor
- Inhibits the conversion of androgen to estrogen with consequent withdrawal of negative feedback effects of estrogen at the hypothalamo-pituitary axis.
- Dose- 2.5 mg OD (Max 7.5 mg)

SURGICAL TREATMENT

- Bilateral ovarian wedge resection- helped in transient reduction in androstenedione and minimal decrease in testosterone levels.
 Instances of POI and infertility were reported hence it was abandoned.
- Laparoscopic ovarian drilling is now recommended for women with BMI<30kg/m^{2,}, no infertility factors other than clomiphene resistance.
- Beneficial effects- sustain for 9 years

Surgical Steps:

- Laparoscopy performed with one primary [10mm] and two contralateral ancillary ports [5 mm).
- Utero-ovarian ligament is grasped using a grasper moving the ovary (towards anterior abdominal wall & in front of uterus)
- Using a double insulated retractable needle electrode connected to a electrosurgical generator & 40 wattage isolated cauterization is undertaken. The number of puncture points depends on the size of the ovary but 4-5 points are sufficient.
- Each crater should be 1-3 mm in diameter and 4 mm in depth

MECHANISM OF ACTION

- Destruction of the ovarian stroma causes
- Marked decrease in circulating levels of androgens namely DHEAS and testosterone [keckstein et al: 1989]
- Decrease in circulating levels of estradiol.
- Reduction in the concentration of immunoreactive LH as well as LH bioactivity. [Ligouri et al:1996]
- Decrease LH/FSH ratio
- Temporary decrease in inhibin levels

Removes intra ovarian block to follicular maturation that precedes ovulation, resulting in recruitment of new cohort of follicles and subsequent ovulation.

Procedure:

- Initially, 10-15 punctures using 100 W current to assist entry and 40 w coagulating current to treat each microcyst over 2 seconds.
- To reduce adhesion formation, cauterisation over 4 points in ovary led to similar pregnancy rate.

RISKS involving LOD:

- Adhesion formation
- Potential surgical risks
- Anesthesia risks
- Premature Ovarian Failure (theoretical complication)



PCOS AND METABOLIC SYNDROME

- About 10 % of women with PCOS develop type 2 diabetes before age
 40 as the rate of progression from glucose intolerance to diabetes is increased.
- Insulin resistance and hyperinsulinemia are associated with chronic low grade inflammation and hypertension
- Hyperandrogenism and obesity each contribute to **dyslipidemia**.

INSULIN RESISTANCE: ASSOCIATES CONDITIONS



Adapted from Consensus Development Conference of the American Diabetes Association. *Diabetes Care*. 1998;21:310-314.

PCOS & CANCER

- Persistently elevated estrogen uninterrupted by progesterone increases the risk of endometrial carcinoma.
- These endometrial cancers are well differentiated, stage 1 lesions with a cure rate of >90%
- Endometrial biopsy should be considered in PCOS patients.
- Risk of ovarian cancer is increased 2 fold to 3 fold in women with PCOS.
- No significant association b/w PCOS and Breast cancer.

KEY MESSAGES

- PCOS is common in adolescents and reproductive age women
- Diagnostic criteria should be clearly documented in each case.
- Management should be as per symptoms, fertility need
- Lifestyle management is definitely the first choice
- Drugs- start with simple and cost effective drugs
- Lap ovarian drilling only when indicated
- Long term care is needed for prevention and early management of long term complications





Thank you