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POLYCYSTIC OVARIAN SYNDROME

In The Adolescent
More has been written about PCOS and less has been understood about it than any other gynecological disorder

- RICHARD LEGRO
Why the problem should be addressed???

• *Girl Child’s appearance is the prime concern for the parents*

• Since PCOS is associated with obesity and hirsutism, depression of child and agony of the parents is of great concern
- HETEROGENEOUS DISORDER
- OVER PRODUCTION OF ANDROGENS
- ANOVULATION
- HIRSUTISM
- INSULIN RESISTANCE
LONG TERM SEQUELAE

- High risk of diabetes
- Obesity
- Metabolic syndrome
- Endometrial hyperplasia
- Anovulatory infertility
- Increased risk for carcinoma of endometrium, ovary and breast
HISTORY OF PCOS

1935 – Stein and Leventhal described the syndrome of amenorrhea, obesity and hirsutism.

1976 – Rebar et al: characterized inappropriate LH secretion in PCOS

1976 – Huffman – series of Adolescent girls with PCOS and hyperandrogenism

1980 – Burghen et al: correlation of hyperandrogenism with hyperinsulinism in PCOS

1985 - Adams et al: critically defines US diagnostic criteria

1999 - Urbank et al: Recognized the familial traits of PCOS, identified the gene defect causing abnormalities
PREVALENCE

• Currently 10% of adolescents
WHY ADOLESCENT ???

During puberty, Multicystic ovaries containing more than six cysts with a diameter > 4mm dispersed throughout ovary occur in normal girls.

This ovarian state is transitory, and reversible, becomes less & less as adolescents begin to ovulate regularly.

So confusing description of cystic ovaries in childhood as polycystic should be abandoned and replaced with

“MULTI CYSTIC OVARIES”
WHAT CAUSES PCOS??

*inciting event not known...........

INTERPLAY OF :-

- GENETIC
- HORMONAL
- ENVIRONMENTAL
• NEURO ENDOCRINE HYPOTHESIS

• ↑ GnRH pulse generator activity
• ↑ pituitary response

• ↑ LH pulse frequency & secretion
• ↓ FSH secretion

• ↑ LH/FSH ratio
(2) OVARIAN HYPOTHESIS

Hyperinsulinemia & insulin resistance

↓ SHBG & IGBF production

Dysregulation of 17 alpha hydroxylase enzyme

↑ androgen production in PCOS

Chronic LH stimulation induces sustained hypersecretion of androgens (testosterone) by the ovaries leading to hyperandrogenism

• Ovarian stroma obtained from hyperandrogenic adolescent has been shown to produce high levels of androgens when exposed to insulin
• A case report of an adolescent who had severe type 2 diabetes & hyperandrogenism
• IV insulin to control blood glucose has shown significant increased levels of androgens, and these androgens returned to baseline when the insulin infusion was stopped
INSULIN RESISTANCE

- MECHANISMS OF INSULIN RESISTANCE:

  ↓ insulin sensitivity in:
  Peripheral tissue ± Liver

  muscle (85%), adipose tissue

*Decreased insulin sensitivity in PCOS appears to be independent of obesity, indicating an intrinsic defect, genetically determined.*

40% OBESE PCOS HAVE IR
10% NON OBESE PCOS HAVE IR
Association between insulin resistance, hyperinsulinemia and clinical manifestations

- Cardiovascular disease risk factors (dyslipidemia, hypertension)
- Impaired glucose tolerance
- Gestational diabetes
- Acanthosis nigricans
- Miscarriage

**Insulin Resistance**

**Hyperinsulinemia**

**PCOS**

- Functional Adrenal Hyperandrogenemia
- Suppression of SHBG synthesis by liver
- Functional Ovarian Hyperandrogenism
- Oligo or Anovulation
- Oligo/Amenorrhea
  - DUB & infertility
  - Endometrial hyperplasia / cancer

- Increase in bio available pool of androgens
- Hirsutism, Acne
- Androgen dependent alopecia
How insulin contributes to hyperandrogenemia?

**DIRECT EFFECT**

↓ SHBG (↑ available androgens)

Binds to IGF receptor on ovary

↑ LH by activating receptor (ovary, adrenal, pituitary)

**INDIRECT**

↑ IGF1 receptor
↓ IGFBP1
↑ available IGF

HYPERANDROGENISM
HEALTH CONSEQUENCES

DIABETES

• Risk increases by:

<table>
<thead>
<tr>
<th></th>
<th>PCOS Women</th>
<th>PCOS Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>7.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>30%</td>
<td>35%</td>
</tr>
</tbody>
</table>

• **2hr Oral Glucose Tolerance Test more sensitive than Fasting Glucose**
OBESITY

- INCIDENCE IS:

<table>
<thead>
<tr>
<th>PCOS Women</th>
<th>PCOS Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>

- Wt is predominantly accumulated in the abdominal area, reflected by INCREASED WAIST TO HIP RATIO

- Obesity leads to obstructive sleep apnea, fatty liver, decreased quality of life
METABOLIC SYNDROME

- Higher incidence of Metabolic Syndrome

- NHANES III (third national health and nutrition examination survey)
  - In control population – 5%
  - PCOS girls – 37%
CARDIOVASCULAR DISEASE

Associated with all the risk factors for CVD

- OBESITY
- DYSLIPIDEMIA
- DIABETES
- INSULIN RESISTANCE
- HYPER ANDROGENEMIA
- INCREASED CAROTID INTIMA – MEDIA THICKNESS
- INCREASED PLASMINOGEN ACTIVATOR INHIBITOR-1
DIAGNOSIS
any **2 OF 3** should be present to diagnose *PCOS* :-

1. **OLIGO AND/OR ANOVULATION**

2. Clinical and/or biochemical signs of **HYPER ANDROGENISM**

3. **POLYCYSTIC OVARIES ON ULTRASOUND** and exclusion of other etiologies (congenital adrenal hyperplasia, androgen secreting tumours & cushing’s syndrome)
Prevalence of polycystic ovarian syndrome in Indian adolescents.


<table>
<thead>
<tr>
<th>Oligomenorrhea</th>
<th>45 days or more, or 8 cycles per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Hyperandrogenism</td>
<td>modified Ferriman and Gallaway’s score of 6 and more</td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td>&gt; 10 cysts, 2-8mm in diameter, volume &gt; 10cucm &amp; echodense stroma</td>
</tr>
</tbody>
</table>
• Prevalence of PCOS in Indian adolescents is 9.13%.

• Early diagnosis in adolescent girls.
<table>
<thead>
<tr>
<th>Sites</th>
<th>Grade-1</th>
<th>Grade-2</th>
<th>Grade-3</th>
<th>Grade-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper lip</td>
<td>Few hairs at the outer margin</td>
<td>Small moustache at outer margin</td>
<td>Moustache extending halfway from outer margin</td>
<td>Moustache extending to mid-line</td>
</tr>
<tr>
<td>Chin</td>
<td>Few scattered hairs</td>
<td>Scattered hairs with small concentrations</td>
<td>Complete cover, light</td>
<td>Complete cover, heavy</td>
</tr>
<tr>
<td>Chest</td>
<td>Circumareolar hairs</td>
<td>Circumareolar hairs with mid-line hair</td>
<td>Fusion of circumareolar hairs with mid-line hair giving three-quarter cover</td>
<td>Complete cover</td>
</tr>
<tr>
<td>Upper back</td>
<td>Few scattered hairs</td>
<td>More than a few scattered hair but still scattered</td>
<td>Complete cover, light</td>
<td>Complete cover, heavy</td>
</tr>
<tr>
<td>Lower back</td>
<td>Sacral tuft of hair</td>
<td>Sacral tuft of hair with some lateral extension</td>
<td>Three-quarter cover</td>
<td>Complete cover</td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>Few mid-line hairs</td>
<td>Rather more but still mid-line</td>
<td>Half cover</td>
<td>Complete cover</td>
</tr>
<tr>
<td>Lower abdomen</td>
<td>Few mid-line hairs</td>
<td>Mid-line streak of hair</td>
<td>Mid-line band of hair</td>
<td>An inverted V-shaped growth</td>
</tr>
<tr>
<td>Upper arm and thigh</td>
<td>Sparse hair growth affecting not more than a quarter of limb surface</td>
<td>More than a quarter coverage but still incomplete</td>
<td>Complete cover, light</td>
<td>Complete cover, heavy</td>
</tr>
<tr>
<td>Forearm and legs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Complete cover, heavy</td>
</tr>
</tbody>
</table>

Forearm and hand, lower leg and feet are not included in the ‘hormonal’ score and only single value is added even when hirsutism involves these extremities bilaterally. Minimum score is zero and maximum is 36. A score of 8 = no hirsutism, 8-16 = mild hirsutism, 17-25 = moderate hirsutism, 25 = severe hirsutism. Values may vary in different ethnic groups.
• **OLIGOMENORRHEA** in adolescent is common in the Physiological maturation of HPO axis
• **HYPERANDROGENISM** maybe the most robust diagnostic criteria in this age group

**PREMATURE PUBARCHE**

• early marker of future PCOS ?????
(Pubic & axillary hair before 8 yrs without any other signs of puberty)

• Early activation could be mediated through marked weight gain and resultant hyperinsulinemia

• Mutation of kinase that phosphorylates Serine causes hyperphosphorylation of 17 alpha hydroxylase enzyme increasing its activity hence resulting in Increased androgen synthesis
DIAGNOSIS

- Oligomenorrhea or Amenorrhoea 2yrs after menarche
- Clinical hyper androgenism (hirsutism, acne)
- Biological hyperandrogenism (elevated plasma testosterone, increased LH/FSH ratio)
- Insulin resistance or hyperinsulinemia (acanthosis nigricans, abdominal obesity, glucose intolerance)
- Polycystic ovaries

Some researchers think that the Rotterdam criteria may overestimate the diagnosis, in the adolescent, however the current definition is the same for adolescents and adults!!!
DIAGNOSIS …Contd

HIRSUTISM
- less marked in adolescents
- duration of exposure to androgen is less
- look for excess hair on upper lip, chin, neck or abdomen

ACNE
- affects only few adolescents with PCOS
- because DHEAS is more than free testosterone
- it is often first sign of hyperandrogenism in the adolescent
Presence of 12 or more follicles

With 2 to 9 mm diameter ovary

Increased ovarian volume greater than 10ml

If only one ovary is affected, it is sufficient to diagnose
**BIOCHEMICAL CHARACTERISTICS**

- ↑↑↑ LH
- Reversed LH : FSH ratio
- High androgen levels, testosterone and Androstenedione
- Normal estrogens
  - estrone > estradiol
- Normal or hyperprolactinemia
- Reduced SHBG
- Hyperinsulinemia
EXERCISE
Promotes fatty acid oxidation and utilization for energy thereby improving insulin sensitivity.
Conditions of excess weight and obesity are increasingly prevalent in developed and developing countries that have adopted a **Western Lifestyle and Diet**.
MANAGEMENT
symptom directed therapy

HIRSUTISM AND ACNE –
Significant issue
Progressive
The sooner it is treated, better is the result

HOW DO YOU APPROACH ??????

✓ Removal of current hair
✓ Suppress the hair growth
✓ Prevent new hair growth
HAIR REMOVING TECHNIQUES

- Waxing
- Plucking
- Shaving
- Depilation
- Electrolysis
- Laser treatment
COMBINED OC PILLS:-

These offer better suppression

- Commonest and effectively controls the symptoms
- Regulates the menstrual cycles
- Prevents endometrial hyperplasia
- Controls hirsutism and acne

**MECHANISM OF ACTION** – primarily

↓ the production of androgens from ovary &
↑ the production of SHBG from liver
↓ LH,
Total testosterone and Androstenedione are ↓
ANTI ANDROGENS

- these work at the **LEVEL OF HAIR FOLLICLE**

- blocks androgen binding to receptors

- inhibits alpha reductase which converts testosterone to DHT

Most commonly used drugs are : -
CYPROTERONE ACETATE

• It is 17 OH progesterone acetate derivative with strong progestogenic properties
• Competes with DHT and testosterone for binding to androgen receptor
• Has anti gonadotrophin effect
• ↓ androgen synthesis by negative feedback effect on the HPO axis activity
FLUTAMIDE (250mg/day in first 10 days) & FINASTERIDE (1-5mg/day)

Are all equally effective in hirsutism treatment.

INHIBIT THE 5 ALPHA REDUCTASE,
Particularly potential at hair follicle level
SPIRONOLACTONE

Combined with OC pills, it is efficacious with a dose of 100 – 200 mg and is usually given in divided doses

Side effects are urinary frequency and postural hypotension

IT INHIBITS DHT BINDING thereby decreasing the androgen production
Role of ethinyl estradiol

- ↑ SHBG &
- ↓ androgens

- ↑ IGFBP
- ↓ androgen bioavailability

- Inhibits 5α-reductase in skin
ABNORMAL BLEEDING

• Goal - regulate menstrual cycle bleeding
• Prevent anemia
• Prevent bleeding accidents
• Prevent long term risk of endometrial hyperplasia

LOW DOSE COMBINED PILLS
PROGESTINS – Also can be given for 10 – 14 days
• 5 – 10 mg medroxyprogesterone acetate
• 5 mg norethindrone acetate
• 100 – 200 mg micronised progesterone for a period of 3 to 6 months
Metabolic correction with Insulin – Sensitizing Agents

METFORMIN

- Biguanide
- developed in 1957
- for the treatment of type II diabetes
- inhibits hepatic glucose production
- Increases peripheral tissue sensitivity to insulin
- At the dose of 1500 to 2000 mg per day in divided doses
- Dosage should be stepped up gradually
- Preferably given after food to reduce side effects
- 3 to 6 months
A randomised placebo control trial in obese adolescent who had PCOS were placed on lifestyle modification

- **Use of Metformin** associated with significant decrease in testosterone
- No change in BMI, cholesterol or insulin sensitivity

Another trial randomized in obese adolescents who had PCOS evaluated with placebo, metformin, oral pills, lifestyle management for 6 months

In the OC pill group, **SHBG was increased and total & free androgens were decreased.**
**N ACETYL CYSTEINE** – Is the acetylated form of the amino acid L–cysteine. Given as a dose of 1200 – 1800 mg/day
- Improves insulin sensitivity
- Significant reduction in insulin levels
- Novel adjuvant to Clomiphene citrate
- Also acts as an anti oxidant

**D CHIRO INOSITOL** – Which contains phosphoglycan which mimics the action of insulin
1200 mg OD for 6-8 wks
- Increases glucose uptake in muscle cells
- Enhances glycogen storage in muscle cells
- Decreases free fatty acids
- Increases insulin sensitivity
SURGICAL THERAPY

Stein-leventhal described ovarian wedge resection as a treatment for anovulation in PCOS women in 1935.

Laparoscopic ovarian drilling is a procedure to correct anovulation and infertility, and should not be used as a first line of treatment for adolescents who have PCOS.
BARIATRIC SURGERY

For those who are unable to lose weight despite multiple attempts, bariatric surgery is the only hope for weight loss.

Morbidly obese adolescents can undergo bariatric surgery if other measures fail to reduce their weight.
S/S of hyperandrogenism & oligo/anovulation

DIAGNOSIS
Physical Exmn, USG & lab tests

PATIENT EDUCATION
1. Lifestyle modification (diet, Exercise, wt reduction)
2. Manage Hirsutism
EXCESS ANDROGEN

Therapy for hirsutism & acne
- Combination OCP
- Cyproterone w/ estrogen
- Finasteride
- GnRH analogues
- spironolactone

ASSOCIATED METABOLIC RISKS
therapy for metabolic risks
- Metformin

LONG TERM FOLLOWUP
Monitor for onset of:
- Dyslipidemia, DM, CV disease, Endometrial Pathology
CONCLUSION

Early Diagnosis & Treatment
Early intervention – better response

• A symptom directed treatment

• **DIET CHANGES, EXERCISE REGIMENS – FIRST LINE OF THERAPY**

• Importance of exercise and thorough counseling should be given to both pt & parents
CONCLUSION ....Contd

• Manual hair removal techniques should be considered
• Referral to a dermatologist for acne
• Hormonal contraception is the first line medical treatment
• Anti androgen therapy, spironolactone can be added to treat hirsutism and acne
• Metformin reserved for insulin resistance pts
• Reassure Adolescents & their parents about ability to have children in future
Thank You

BETI BACHAO, BETI PADHАО