Metabolic consequences of Polycystic ovary syndrome (PCOS)

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Date: 15/07/2016
What is PCOS?
Stein and Leventhal in 1935

PCOS

Symptoms

- Obesity
- Hirsutism
- Virilization
- Cyclic Menses
- Abnormal menses
- Amenorrhea
- Dysmenorrhea
- Biphasic BBT
- Infertility

There are approximately 103,000 citations in a Web of Science (Thomson Reuters, New York, NY) Citation Report for 1980–2011 on the topics of PCOS or hyperandrogenism and hyperinsulinemia, insulin resistance, glucose intolerance, or diabetes mellitus. The annual citations have increased steadily from 1 in 1980 to approximately 12,000 in 2011.

600 articles in QR of AE-PCOS

Diamanti-Kandarakis E, and Dunaif A Endocrine Reviews 2012;33:981-1030
PCOS: changing women’s health paradigm

Metabolic disease

Reproductive disorders

(young age)
- menstrual disorders
- hirsutism
- contraception
- sexual health
- infertility

(older age)
- pregnancy complications
- quality of life
- type 2 diabetes
- cardiovascular disease
- cancer risk?

Multi-disciplinary approaches

Bart C.J.M. Fauser, Basil C. Tarlatzis, Robert W. Rebar, Richard S. Legro, Ada Consensus on women’s health of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Workshop Group
How common is PCOS?

- PCOS affects 5-10% women in West
- 2-4% in Europe
- 19-21% in India.. parallel to DM prevalence
India is also a PCOS capital? Parallels PCOS
India vs. World

1. Elevated inflammatory markers
2. Insulin resistant
3. Central obesity
4. More fat mass
5. Less lean mass
How do you diagnose PCOS?

**PCOS Findings**

- **Physical**
  - Obesity
  - Hirsutism
  - Acanthosis
  - Abnormal menses
  - Acne

- **Biochemical**
  - ↑ Androgen
    - Testosterone
    - DHEAS
    - Androstenedione
    - 17OH progesterone
  - ↓ SHBG
  - ↑ LH
  - Insulin/Glucose
  - ↑ PAI-1
  - ↑ Lipids

- **Ultrasound**
  - Necklace sign
  - ↑ Ovarian volume
  - Antral follicle count
  - Doppler blood flow changes

**Spectrum of PCOS**

- Oligomenorrhea / amenorrhea
- Clinical / biochemical features of hyperandrogenism
Multiple necklace cysts

- Cysts are not must for diagnosis.
- They have no consequences

Original Article

Comparative evaluation of sonographic ovarian morphology of Indian women with polycystic ovary syndrome versus those of normal women

Sanjeed Ahmed, Shivani Pahwa², Chandan Jyoti Das, Farooq A Mir, Sobia Nisar², Majid Jehangir, Shamceem Parveen, Aafia Rashid, Mohd Ashraf Ganic
How does PCOS present?
The Dual Ordeal

The Outlook
- Obesity
- Acne
- Hirsutism
- Alopecia

The inside story
- Cycle disturbances
- Infertility
- Insulin resistance
- Glucose intolerance
- Dyslipidemia
- Premalignant
ICE BERG SYNDROME?

50% Don’t know

90% don’t know metabolic issues
Menstrual disturbances

Normal cycles <35 days interval or >8 cycles in a year

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. PCOS</th>
<th>No. of PCOS patients with oligoamenorrhea</th>
<th>PCOS patients with oligoamenorrhea (%)</th>
<th>No. of PCOS patients with eumenorrhea</th>
<th>PCOS patients with eumenorrhea (%)</th>
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<tbody>
<tr>
<td>Ferriman and Purdie, 1983</td>
<td>280</td>
<td>237</td>
<td>84.6</td>
<td>43</td>
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<td>Ardaens et al., 1991</td>
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<td>Rajkhowa et al., 1995</td>
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<td>129</td>
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<td>Balen et al., 1995</td>
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<td>Falsetti and Eleftheriou, 1996</td>
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<td>Alborzi et al., 2001</td>
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<tr>
<td>Total</td>
<td>5659</td>
<td>4437</td>
<td>78.4</td>
<td>968</td>
<td>18.1</td>
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</tbody>
</table>

Indicator of no egg shedding (Ovulation)- Infertility
Unwanted hair growth
Hirsutism scoring

Modified Ferrima-Gallwy method 1930

Each area = 1-4

Total score = 36  Significant > 8
Male pattern hair & Pimples

High male hormone (testosterone)
High serum insulin levels (Insulin resistance)

Velvety black Patches (Acanthosis Nigricans)
Metabolic abnormalities

- Obesity - CENTRAL
- High serum insulin (Hyerinsulinemia)
- High Blood sugar (Glucose intolerance / Diabetes)
- High cholesterol (Dyslipidemia)
- High uric acid (Hyperuricemia)
- Fatty liver (NASH)
- Heart problems (Coronary artery disease)
- Protein loss from Kidney (Premicroalbuminuria)
- Increased sleep problems (OSA)
- Strokes
- Hyperhomocystenemia
- CANCERS – breast, endometrium, ovarian
Prevalence of glucose intolerance among adolescent and young women with polycystic ovary syndrome in India

Ganie M. Ashraf*, M.L. Khurana*, M. Eunice*, N. Gupta*, S.N. Diwivedi**, M.S. Gulati***, A.C. Ammini*

Current PCOS Series
(Mean age =23 years)

SKIMS
DM= 4.3%
IGT=6.53%
IFG=17.97%
Total=28.38%

Half have pre-diabetes or Diabetes

Mean age of 23 years

• DM 8.93% IFG 29.16% IFG 3.57%
Ultrasonographic prevalence of PCO was higher in women with diabetes than in non-diabetic (61.0% vs. 36.7%)
PCOS - 50-60 % are OBESE
Metabolic syndrome vs. PCOS

• The prevalence of MS in PCOS by IDF, WHO, ATP III and criteria were 50.0%, 47.3% and 23.68% respectively.
• ATP III criteria grossly underestimates the MS prevalence

Ganie MA, Kamili MMA et al Diabetes & CVD
Prevalence of metabolic syndrome in the family members of women with polycystic ovary syndrome from North India

Iram Shabir, Mohd Ashraf Ganie¹, Mohd Afzal Zargar², Dilafoz Bhat³, Mohd Muzzafar Mir⁴, Aleem Jan⁵, Zaffar Amin Shah⁶, Vicar Jan⁶, Riyaz Rasool⁷, Andleeb Naqati²
Elevated hsCRP/MCP-1 / Resistin / ICAM / PAI-1 with higher levels of adiponectin and F VIII levels

Pattern of urinary albumin excretion in normotensive young and adolescent Indian women with polycystic ovary syndrome


Departments of Endocrinology, Nephrology, and Immunology and Molecular Medicine, Sheri-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, 1Department of Clinical Biochemistry, University of Kashmir, Srinagar, Jammu and Kashmir, India, 2Departments of Gastroenterology, and Clinical Biochemistry, Al Jouf, Aljouf University, KSA, 3Sheri-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, 4Department of Endocrinology, Sheri-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

**ABSTRACT**

**Objective:** Polycystic ovarian syndrome (PCOS) is a clinically heterogeneous endocrine disorder affecting up to 4–8% of women of reproductive age. The aim of this study was to evaluate the presence of microalbuminuria in women with PCOS and study its correlation with the various metabolic, clinical, and hormonal parameters. **Materials and Methods:** A cross-sectional study involving 69 PCOS women was carried out in a tertiary care center hospital. The diagnosis of PCOS was made according to the Rotterdam
Atherosclerotic disease accounts for most of the excess mortality in patients with diabetes.

Aggressive anti-atherosclerotic intervention is warranted in diabetics.
Dyslipidemia

↑ TGs

↓ HDL

Small dense LDL
Sleep Apnea and PCOS

- Multiple groups have documented an increased risk

Fatty liver - 30-40%

Cancers – uterus, breast

Body Image and Quality of Life in PCOS
N=112 PCOS girls
72% have some psychiatric abnormality
No eating disorder

Ganie M A et al 2010
Macrosomia - GDM
A Complex Metabolic Disorder

Hyperandrogenism

Reproductive dysfunction

Macrovascular complications

“INSULIN RESISTANCE SYNDROME”

Central obesity

Malignancies

Dyslipidemia

Hypertension

Original Article

Prevalence of metabolic syndrome in the family members of women with polycystic ovary syndrome from North India

Iram Shabir, Mohd Ashraf Ganie¹, Mohd Afzal Zargar², Dilafriz Bhat³, Mohd Muszafar Mir⁴, Aleem Jan¹, Zaffar Amin Shah⁵, Vicar Jan⁶, Riyaz Rasool⁷, Andleeb Naqati³
Genetic influences

Environmental effects

In utero

Childhood

Adulthood

Cause -??- Multiple factors –LIFETSYLE DISORDER

Toxicants/ Insults

Genetic influences

Environmental effects
Evolution of Obesity:

- **>10,000 B.C.**: last Ice age ended
- **7,000 B.C.**: Wheat cultivated
- **1900 A.D.**: Coca Cola
- **1960s**: Fast foods/McDonald
- **1970s (1980)**: TV
- **1980s (1990)**: Computer, video games
Environmental ‘Endocrine Disruptors’ (EDs)

Industrial

Natural

Intentional

Unintentional

Pharmaceutical
Brothers and sons of PCOS SUBJECTS – high prevalence of Metabolic syndrome

PCOS variants also occur in sibs of subjects

Syndrome XX (Dunaif 2005)

Sex-limited Reaven's syndrome
Management

Focuses to reverse
– basic pathophysiology ??

1. Lifestyle modification
2. Insulin sensitizers – Metformin / Glitazones
3. Anti-androgens – Flutamide, Spironolactone
4. Anti-obesity – Sibutramine, Orlistat
5. Ovulating agents – Clomiphene, Letrozole
6. Others – inositol, acupuncture, Chinese medicine etc
Prevention is the Key

If we work out the burden and its cost on healthcare- Enormous

Editorial

Polycystic ovary syndrome – A metabolic malady, the mother of all lifestyle disorders in women – Can Indian health budget tackle it in future?

M. Ashraf Ganie, Sanjay Kalra

Department of Endocrinology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, 1Department of Endocrinology, Bharti Hospital and BRIDE, Kamal, Haryana, India
30 minutes brisk walk daily

Upper Body Exercise

Upper body weight routine (A) Curls/palms up (B) Reverse curls/palms down (C) Bent knee over rows (D) Tricep kick-backs (E) Side lift (F) Military press

Yoga- MAY HELP
Dietary advice

- Qualified dietician
- Low fat / low carbohydrate
- High protein
- High fibre
- According to your BMI / Weight

5-10% WEIGHT LOSS
Menstrual regulation/ Fertility

- MEDROXYPROGESTERONE ACETATE: 5 to 10 mg/day for 10 to 14 days monthly.
- OCP – Mala D/ Ovral etc.

Conception – Clomifene -=90%
IVF
Androgenic Symptoms

Hirsutism, acne, and alopecia

COSMETIC TREATMENT:
- depilatories, waxing, shaving for hirsutism
- laser hair removal and electrolysis.
- Side effects: treatment-site irritations.

ANTIANDROGENS.
- Spironolactone, at a dose of 25 to 100 mg twice daily, is the most commonly used antiandrogen because of its safety, availability, and low cost.
- Because of the increased risk of teratogenicity, contraception is recommended when patients are using antiandrogens.
- Spironolactone 100/ flutamide 25/ finasteride 5 found equally effective.

ORAL CONTRACEPTIVES:
- Estrogen and progesteron/antiandrogen combination are the primary OCP used in combination of hirsutism, acne, irregular periods.
- Combination of antiandrogen / OCPs for synergy.
Addressing metabolic problems

Need to decrease – insulin
- testosterone
Insulin Sensitizers

**Metformin**
“the French lilac: exercise mimetic”

**Liver, skeletal muscle**

- ↓ glucose b/s
- ↓ gluconeogenesis
- ↑ glucose uptake

**AMPK**
(AMP activated kinase)

**AMP:ATP Balance**

- ↓ lipolysis
- ↓ lipogenic gene expression

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**Pioglitazone**
Anti-androgen

- Spironolactone
  -- Cyproterone acetate
  -- Flutamide
  -- Finasteride
Drug Combinations

- OCP with Pioglitazone
- Metformin with OCP
- Metformin with Spironolactone

Improved efficacy of low dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six month, open label randomized study

Mohd Ashraf Ganie, M.D.; D.M, Associate Professor, Madan Lal Khurana, PhD, Scient Sobia Nisar**, M.D, Senior Resident, Parvaiz Ahmed Shah**, M.D, D.M, Professor, Zaffar Amin Shah*, PhD, Additional Professor, Bindu Kulshrestha****, MD; DM, Assistant Professor, Nandita Gupta, PhD, Professor, Mohd Afzal Zargar #, PhD, Professor, Tariq Ahmed Wani ***, M Sc, Biostatistician, Syed Mudasir @, PhD, Additional Professor, Farooq Ahmed $, M.D, Senior Resident, Shenaz Taing **, MD, Associate Professor

Departments of Obstetrics and Gynecology*, Internal Medicine**, Govt. Medical College, Clinical biochemistry University of Kashmir**, Clinical biochemistry@, Biostatistics, ***, Radio diagnosis $, Immunology and Molecular Medicine*, Sheri-Kashmir Institute of Medical Sciences, Srinagar, J & K; Department of Endocrinology RML Hospital****, and, Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, Ansari Nagar, New Delhi–29, India.
# Suggested Screening in PCOS

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Recommendation</th>
<th>Minimum frequency</th>
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<tbody>
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<td>Glucose tolerance</td>
<td>2-h oral GTT</td>
<td>• Every 2 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Annually if PCOS and additional risk factors</td>
</tr>
<tr>
<td>Cardiovascular risk</td>
<td>Body mass index</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>Waist circumference</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>Smoking status</td>
<td>At each visit</td>
</tr>
<tr>
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<td>Physical activity status</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>(and advice)</td>
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<tr>
<td></td>
<td>Blood pressure</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>Lipid profile</td>
<td>Annually if abnormal or obese. Every two years if found normal.</td>
</tr>
</tbody>
</table>

*British Journal of Diabetes and Vascular Disease. 2013;13(3):115-123*
SUMMARY & CONCLUSION

PCOS is a common and on rise- tip of iceberg

Constellation of metabolic abnormalities

- PCOS-METABOLIC SYNDROME - PRE DIABETES – DM
- Global approach – both its current clinical issues and long-term metabolic consequences
- Life style modification to re-enforce the importance of weight loss
- Pending the understanding pathogenesis – IDS, AA
- Metformin – drug of choice – metabolic abnormalities
- Lipid, NASH, Obesity, Psychiatric disorders - need data
Metabolic Syndrome, Pre-diabetes and PCOS Society

MP-PCOS

(M. P. PCOS)

mppcos.society@gmail.com
Thanks