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Head, Division of Reproductive medicine at Manipal University
National Vice President of the Federation of Obstetrics and Gynecology for the year 1999.
Inspector, Examiner and Advisor, National Board of Examinations
Examiner of Undergraduates and Postgraduates in several universities
Appointed on the Editorial committee of several journals
Has more than 300 publications and presented more than 675 presentations in National and International congresses
Editor of ten Text books.
President, Karnataka State obst and gyn societies of FOGSI [The Federation of Obstetrics & Gynaecological Societies of India](2011-12)
Awarded the FOGSI – Dr Kutty Lifetime Achievement Award for 2011-12
Member of Task force of Human Developmental & Disease Biology, Department of Biotechnology, New Delhi
Member of the Project Review Group (PRG) on Reproductive and Child Health – Indian Council of Medical Research, New Delhi.

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Other pathologies in PCOS

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Greetings From University Town - Manipal

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PCOS Bengaluru 2017
Polycystic ovarian syndrome

- Endocrine disturbances
  - Acne
  - Hirsutism
  - Infertility
- Reduced quality of life
  - Hypertension
  - Anxiety
  - Depression

- Other diseases
  - Endometrial hyperplasia
Polycystic Ovary Syndrome May Be an Autoimmune Disorder – Review article

- Low level of progesterone in PCOS → overstimulation of immune system → more estrogen → various autoantibodies

Different autoantibodies have been documented in PCOS
- anti-nuclear (ANA),
- anti-thyroid, antispermatic,
- anti-ovarian, and
- anti-islet cell antibodies.
- anti-TPO that have been documented in systemic lupus erythematosus and Hashimoto thyroiditis

Hifsa Mobeen, Nadeem Afzal, and Muhammad Kashif Department of Immunology, University of Health Sciences, Pakistan
Scientifica Volume 2016
Autoimmunity

- Autoimmunity is characterized by induction of autoreactive cells (e.g., B cells, T cells) and proteins (e.g., antibodies).
- Autoimmunity is classified as
  - **Organ specific** (Grave’s disease, Hashimoto’s thyroiditis, and IDDM)
  - **Non organ specific** (systemic autoimmunity are SLE, rheumatoid arthritis, rheumatic fever)
Increased TRH from hypothalamus

Up-regulation of effector T-cells
Down-regulation of regulator T-cells

Increased Leptin

Raised TSH

Adiposity

Autoimmunity
Autoimmunity in PCOS
Normal menstrual cycle

**Follicular phase**
- Estradiol: Increase
- Interleukin 6: Increase

**Luteal phase**
- Progesterone: Decreased
- Interleukin 6: Decreased

**PCOS**
- Oligo/anovulation
- Low progesterone
- Persistent high interleukin 6
Interleukin 6

Stimulates Naïve T cells

TH-17 cells

Inhibits TGF Beta induced TREG cells

TREG cells prevent excess effector T cell responses

TH-17 cells are key players in pathogenesis of autoimmunity and protection from bacterial organs
High estrogen in PCOS effects

- IL-6 has a very important role in regulating the balance between IL-17-producing Th17 cells and regulatory T cells (Treg).
- Th17 cell is a key player in the pathogenesis of autoimmune diseases and protection against bacterial infections, while Treg functions to restrain excessive effector T-cell responses.
- Dysregulation or overproduction of IL-6 leads to autoimmune diseases in which Th17 cells are considered to be the primary cause of pathology.
Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism


26 patients with untreated hypothyroidism
PCOS (n=10), normal-appearing (n=16) ovaries and 20 euthyroidic controls

Conclusions:
• A decrease in ovarian volume,
• resolution of ovarian cysts and
• reversal of the polycystic ovary syndrome-like appearance, together
• with improvement in serum hormone levels, occurred after euthyroidism was achieved
Subclinical hypothyroidism is associated with metabolic syndrome and clomiphene citrate resistance in women with PCOS

The prevalence of CC resistance (30.4%), IR (43.5%) and MS (34.8%) in the Subclinical hypothyroidism group was significantly higher than that in the EU group (p < 0.05).

**Conclusion:**

There was a relationship between
• Subclinical hypothyroidism,
• Metabolic syndrome and
• The response to clomiphene citrate (CC) stimulation in women with PCOS
Impact of elevated thyroid-stimulating hormone levels in polycystic ovary syndrome


- 583 women with PCOS, 125 women (21.4%) had thyroid disturbances
- 109 women, subclinical hypothyroidism.

Patients with elevated TSH levels had significantly
- increased fasting insulin,
- insulin resistance, and
- total cholesterol (TC)/high-density lipoprotein cholesterol (HDL) ratio and
- lower free thyroxin, insulin sensitivity and HDL

(p < 0.05 for all)

continued....
Impact of elevated thyroid-stimulating hormone levels in polycystic ovary syndrome (contd..)


- Euthyroid PCOS women with thyroid hormone substitution showed significant differences in TSH, age, body mass index, HDL and systolic blood pressure compared to those without hormone replacement therapy

Conclusions:

- Hypothyroid disturbances and elevated TSH levels are common findings in PCOS, which are associated with an adverse metabolic profile

- Therefore, women with diagnosed PCOS should be screened for thyroid dysfunction
Polycystic ovary syndrome and Chronic Autoimmune Thyroiditis (AIT)


- The prevalence of subclinical hypothyroidism (SCH) in women with PCOS was 16.9% and 6.2% in the non-PCOS group
- AIT was more common in the PCOS group compared with the non-PCOS group (43.1% versus 26.2%)

CONCLUSION:

- AIT risk was similar in the PCOS and the non-PCOS group
- SCH are more common in women with PCOS, highlighting a need for periodic monitoring of thyroid function
Polycystic ovary syndrome and risk of uterine leiomyomata


a Slone Epidemiology Center, Boston University, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

b Center for Uterine Fibroids, Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

Result(s)—During 114,373 person-years of follow-up, 3,631 new cases of UL confirmed by ultrasound (N = 2,926) or hysterectomy (N = 705) were reported. After adjustment for potential confounders, the incidence of UL was 65% higher among women with PCOS than women without PCOS.
Uterine leiomyoma (UL)

- Although UL are thought to be influenced primarily by endogenous levels of estrogens and Progesterone, there is a growing body of literature to suggest that elevated LH levels, independent of ovarian function,

- dysregulation of the insulin-growth factor and growth hormone (IGF-GH) axis, may be important in the etiology of UL
The cross-sectional Uterine Fibroid Study of the National Institute of Environmental Health Sciences (NIEHS) found a positive association between urinary LH levels and risk of UL, particularly for large tumors.

Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review

Holly R. Harris¹,²* and Kathryn L. Terry²,³
Coexistence of polycystic ovary syndrome and endometriosis in women with infertility

Kristin J. Holoch et al J Endometr Pelvic Pain Disord 2014; 6(2): 79 - 83

- In this case-control study, a significant association between endometriosis and women with PCOS with pelvic pain and/or infertility was found
- The majority of endometriotic lesions (76%) were stage I or II
This study has, for the first time, identified a panel of six proteomic biomarkers that were similarly overexpressed in women with OC and PCOS (calreticulin, fibrinogen-g, superoxide dismutase, vimentin, malate dehydrogenase, and lamin B2). Five of these biomarkers were identified in the same tissue in women with PCOS as in OC (ovarian tissue).
It is difficult to advance a single unifying hypothesis on a common pathway through which these six biomarkers could link PCOS to Ovarian cancer without further confirmatory studies.

- Some of these biomarkers could have been identified by chance, and this underpins the need for future research, data synthesis, and meta-analysis as consistent with standard scientific practice.
According to the ultrasound findings, women were allocated to three groups:
- 351 out of 456 showed normal-appearing ovaries (group A),
- 93 had polycystic-appearing ovaries/PCO (group B) and
- 12 had PCO syndrome (group C).

- In group A, 24 (6.83%) women showed breast pathology.
- In group B, there was an association between PCO and breast pathology in 53 (56.98%) women,
  while in group C it was noted in 11 out of 12 (91%).

**Conclusion:** This study showed a significant association between PCO and benign pathology. This should encourage the performance of a screening breast sonography on women with PCO.
Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review

Holly R. Harris1,2* and Kathryn L. Terry2,3

Harris and Terry Fertility Research and Practice (2016) 2:14

• The association with ovarian cancer was less clear, but a potentially increased risk of the borderline serous subtype was reported by two studies.

• No consistent association between PCOS risk and breast cancer was observed.

• Conclusion: The associations between PCOS and endometrial, ovarian, and breast cancer are complex, with the need to consider many methodological issues in future analyses. Larger well-designed studies, or pooled analyses, may help clarify these complex associations.
Is PCOS an inflammatory process?

Antoni J. Duleba, M.D. and
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Anuja Dokras, MD., PhD
University of Pennsylvania, Philadelphia, USA. Obstetrics and Gynecology, 3701 Market Street, Philadelphia, PA 19104 (ADokras@obgyn.upenn.edu)
**PRO--** PCOS is associated with low-grade systemic inflammation as evidenced by elevation of multiple markers of inflammation such as

- C-reactive protein,
- interleukin-18,
- monocyte chemoattractant protein-1 and
- white blood count as well as
- endothelial dysfunction and increased oxidative stress.

**CON--** The evidence in support of the presence of chronic inflammatory state in the majority of women with PCOS is incontrovertible.

- It is apparent that PCOS is associated with a significant elevation of multiple markers of inflammation including CRP, IL-18, MCP-1, and white blood count.
PCOS and inflammation...

• Furthermore, PCOS is associated with other derangements associated with inflammation such as increased oxidative stress and endothelial dysfunction.

• While the etiology of systemic inflammation in PCOS remains unclear, recent data raise the intriguing possibility of a link between PCOS, inflammation and chronic low grade infectious agents such as Chlamydia pneumoniae, Helicobacter pylori and pathogens inducing periodontal inflammation.
PCOS and inflammation...

Literature evaluating the role of pathogens in PCOS is still minimal but suggests a possible association of this syndrome with *Chlamydia* species, *Helicobacter pylori* and periodontal disease.
Polycystic ovary syndrome and mental disorders: a systematic review and exploratory meta-analysis

Conclusion
- Results from this systematic review indicate that specialized literature shows a lack of data on the association of PCOS and mental disorders.
  - Only six studies were selected and even these used heterogeneous concepts of assessment.
  - Individuals with PCOS showed a greater prevalence of anxiety and depressive symptoms.
The association between polycystic ovary syndrome and ectopic pregnancy after in vitro fertilization and embryo transfer

Jind Wang et al AJOG August 2013 Volume 209, Issue 2, Pages 139

• 5339 women who had clinical pregnancies after in vitro fertilization treatment (PCOS, 205 women; non-PCOS, 5134 women) at Nanjing Medical University (China) between 2007 and 2011

• High estradiol group (>4085 pg/mL) had higher ectopic pregnancy rates compared with the low estradiol group (≤4085 pg/mL; 3.4% vs 2.0%)

• with PCOS appear to hold a lower threshold of hyperphysiologic estradiol level that triggers the occurrence of ectopic pregnancy after COH
Conclusion

PCOS and other pathologies

• There seem to be a lot of conditions associated with PCOS
• Finally, a knowledge of the possibility of developing of these has to be borne in mind of a treating physician
Thank you