

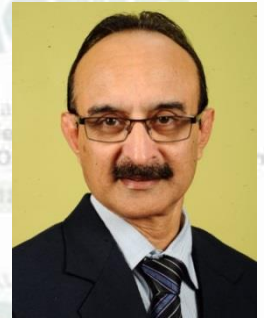
Dr Pratap Kumar

Professor

Department of Obstetrics and Gynaecology

Kasturba Medical College

Manipal University, Manipal - 576 104 (Karnataka, India)



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

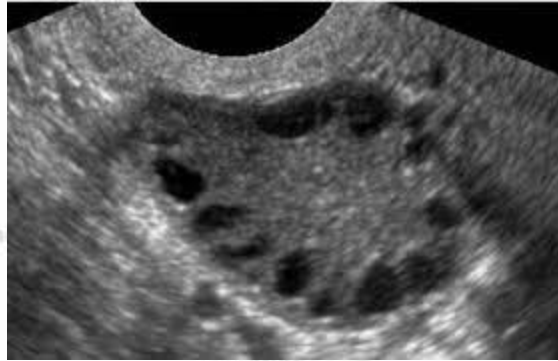
Member of Task force of Human Developmental & Disease Biology, Department of Biotechnology , New Delhi

Member of the Project Review Group (PRG) on Reproductive and Child Health – Indian Council of Medical Research, New Delhi.

8/31/2017



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Other pathologies in PCOS

Prof Pratap Kumar
Obstetrics and Gynecology
Kasturba Medical College
Manipal University
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INDIA

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Dates: June 16 - 18, 2017 | Bengaluru

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Greetings From University Town -Manipal

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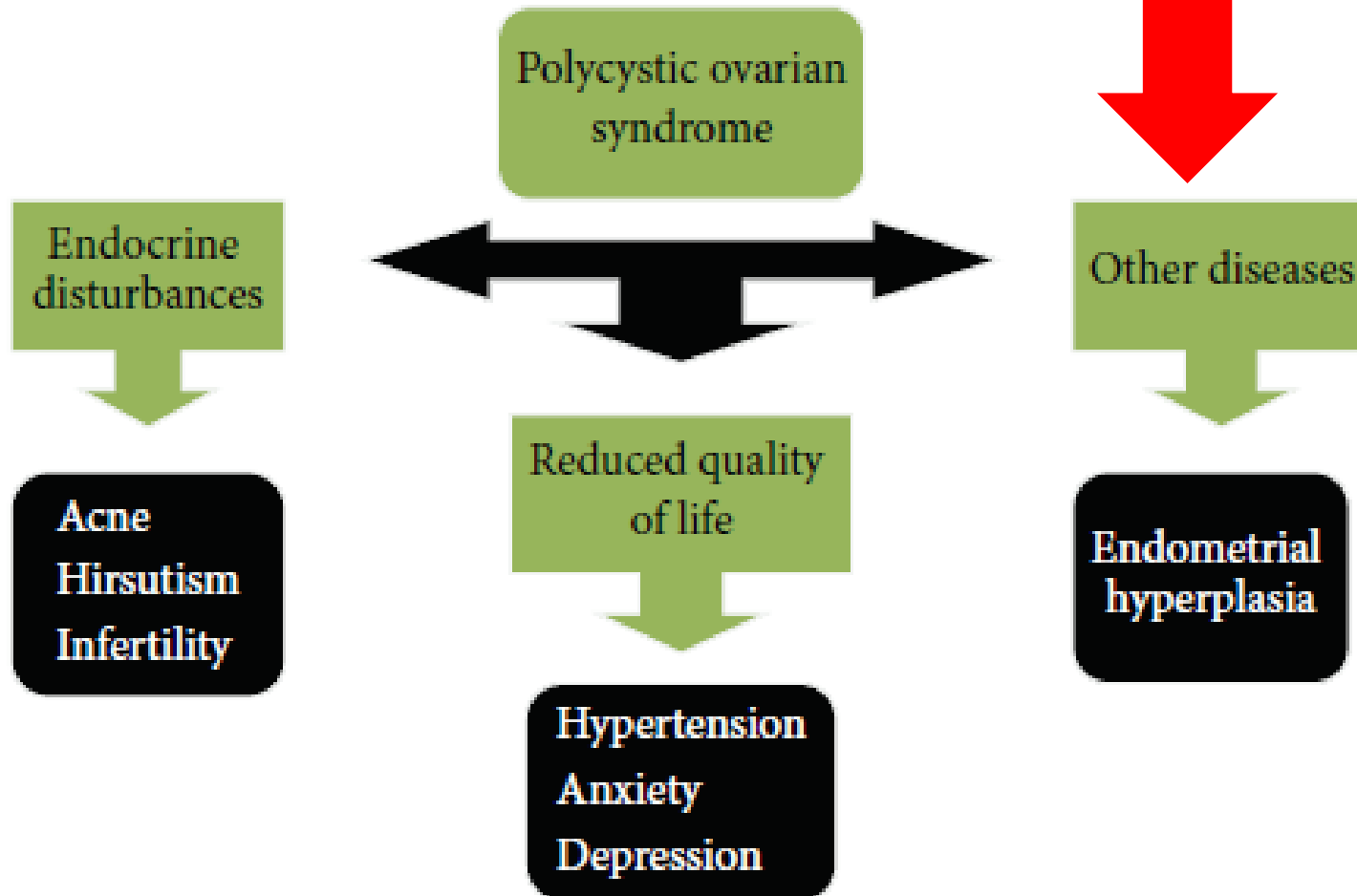
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Polycystic Ovary Syndrome May Be an Autoimmune Disorder – Review article

- 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 Scientific Volume 2016

Autoimmunity

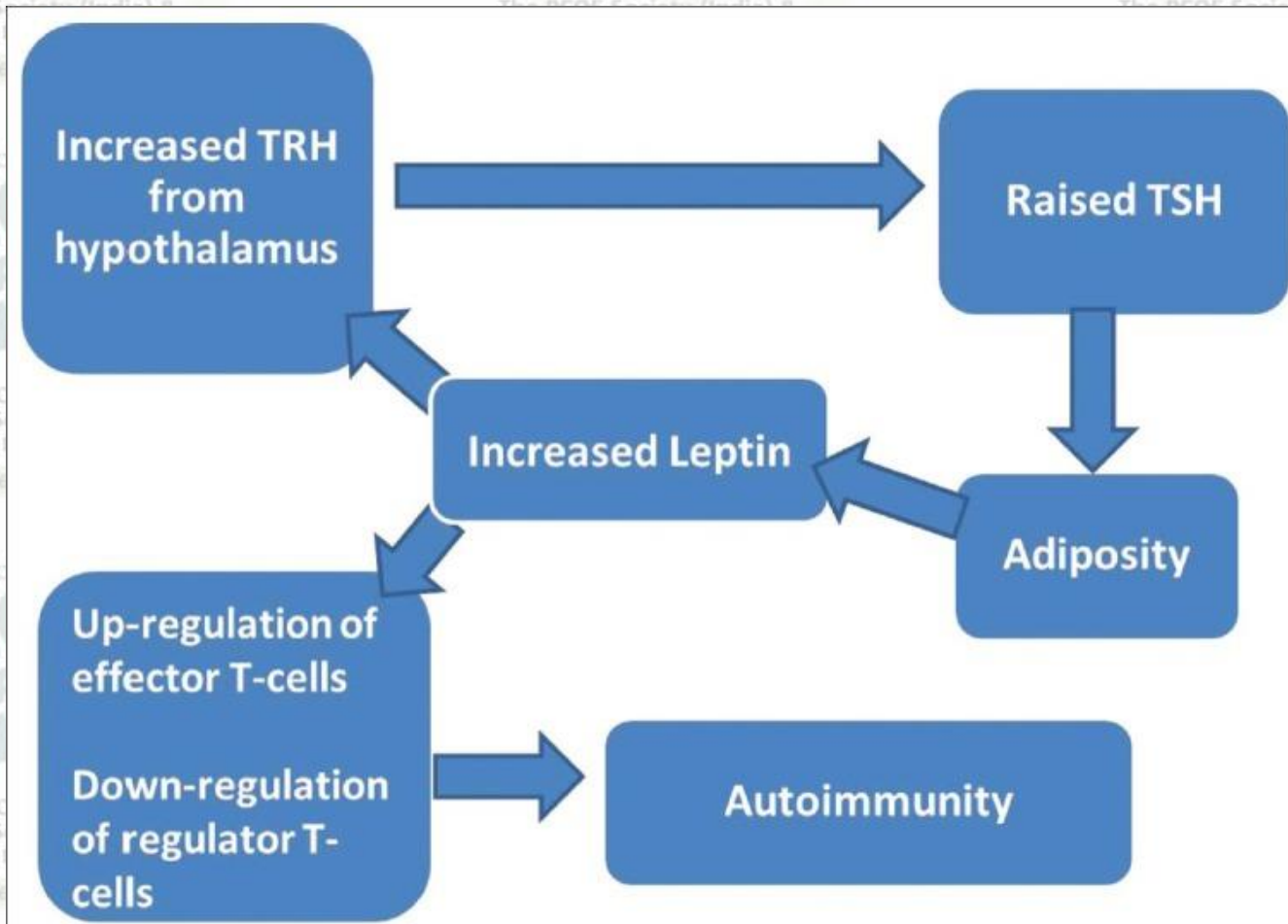
- Autoimmunity is characterized by induction of autoreactive cells (e.g., B cells, T cells) and proteins (e.g., antibodies).
- Autoimmunity is classified as

Organ specific

(Grave's disease, Hashimoto's thyroiditis, and IDDM and

Non organ specific

(systemic autoimmunity are SLE, rheumatoid arthritis, rheumatic fever)





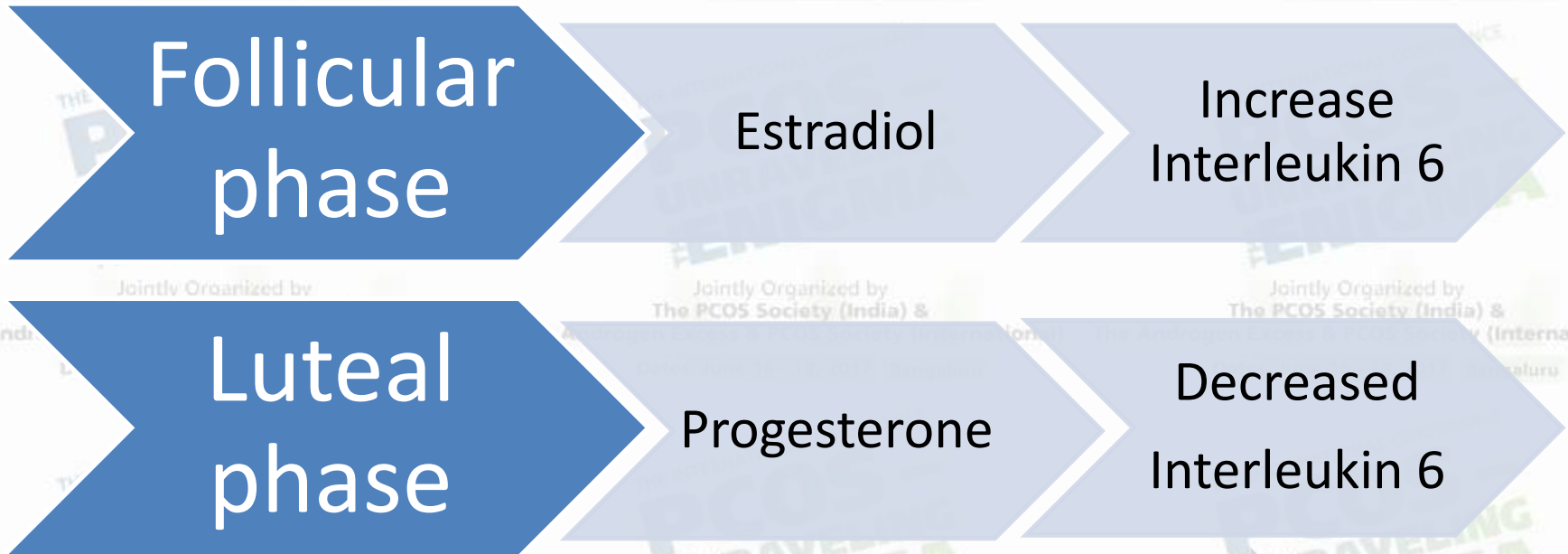
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Autoimmunity in PCOS

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Normal menstrual cycle



PCOS

Oligo/anovulation

Low progesterone

Persistent high interleukin 6

Pathogenesis of autoimmunity

Interleukin 6

Inhibits TGF
Beta induced
TREG cells

TREG cells
prevent excess
effector T cell
responses

Stimulates
Naïve T cells

TH-17 cells

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

Muderris et al Ann Saudi Med 2011 Mar-Apr;31(2):145-51

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

Lu YH et al Gynecol Endocrinol 2016 May 12:1-4.

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

Trummer C et al Gynecol Endocrinol 2015 Oct;31(10):819-23

- 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..)

Trummer C et al Gynecol Endocrinol 2015 Oct;31(10):819-23

- 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)

Novais Jde S et al *Gynecol Endocrinol*. 2015 Jan;31(1):48-51.

- 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



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Fertil Steril. Author manuscript; available in PMC 2007 May 24.



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Published in final edited form as:

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Polycystic ovary syndrome and risk of uterine leiomyomata

Lauren A. Wise, Sc.D.^a, Julie R. Palmer, Sc.D.^a, Elizabeth A. Stewart, M.D.^b, and Lynn Rosenberg, Sc.D.^a

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

Baird DD, Kesner JS, Dunson DB. Luteinizing hormone in premenopausal women may stimulate uterine leiomyomata development. J Soc Gynecol Invest 2006;13:130–5.

Harris and Terry *Fertility Research and Practice* (2016) 2:14
DOI 10.1186/s40738-016-0029-2

Fertility Research and Practice

REVIEW

Open Access



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

Holly R. Harris^{1,2*} and Kathryn L. Terry^{2,3}

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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



Proteomic biomarkers for ovarian cancer risk in women with polycystic ovary syndrome: a systematic review and biomarker database integration

Nicolas Galazis, B.M.B.S.,^a Olalekan Olaleye, F.M.C.O.G.,^a Zeina Haoula, M.R.C.O.G.,^a Robert Layfield, Ph.D.,^b and William Atiomo, D.M.^a

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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).

Proteomic biomarkers....

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

Association between Polycystic Ovary and Fibrocystic Breast Disease

D'Amelio R. · Farris M. · Grande S. · Feraudo E. · Iuliano A. · Zichella L.

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. Harris^{1,2*} and Kathryn L. Terry^{2,3} 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.



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Is PCOS an inflammatory process?

Antoni J. Duleba, M.D. and

Department of Obstetrics and Gynecology, University of California Davis, 4860 Y Street, Sacramento, CA 95817 (ajduleba@ucdavis.edu).

Anuja Dokras, MD., PhD

University of Pennsylvania, Philadelphia, USA. Obstetrics and Gynecology, 3701Market Street, Philadelphia, PA 19104 (ADokras@obgyn.upenn.edu)

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PCOS and Inflammation...

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

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
8 November 2016

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 olume 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

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