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POLYCYSTIC OVARIAN SYNDROME: AN ENCHANCING RISK FACTOR FOR CANCER

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is the commonest endocrinological disorder leading to reproductive as well as metabolic dysfunction in the women. It's the most frequent illness impacting women of reproductive age including PCOS or multi-cystic ovaries, Stein Leventhal syndrome, Schlerocystic ovaries. PCOS jeopardizes feminine identity of a woman due to alteration in her aesthetic standards in the form of hirsutism, acne, alopecia, obesity, menstrual irregularities, infertility and many more complications. Studies suggest that hyperandrogenism, hyperinsulinemia, genetic, epigenetic, and environmental factors all could be considered as the major factors aggravating the disease. Women with Pcos are at increased risk of developing different types of cancer especially that of endometrial, ovarian and breast cancer. Unopposed estrogen exposure may be the prominent risk factor for the upcoming disaster. This review paper, will highlight the possible correlation between PCOS and cancer and how it could together trigger the cancer progression and metastasis.

Objectives:

- To assess the association between PCOS and cancer especially endometrial, ovarian and breast cancer.
- To explore the relationship between genetic, enivornmental and other factors that may explain PCOS and its cancer risk.
- To overcome PCOS and to prevent /reduce the risk of developing cancer.

Highlights:

- Potential risk factors for PCOS, endometrial, ovarian and breast cancer.

KEYWORDS: PCOS, cancer, harmones, lifestyle.

INTRODUCTION

PCOS[1] is an multifactorial syndromic disorder that impacts women of reproductive age worldwide. High ratio of LH to FSH & increased frequency of GNRH are possible causes, but exact pathology behind this syndrome is unknown. Role of external and internal factors play an important role in development of this epidemic including insulin resistance, hyperandrogenism, environmental, genetic factors, and epigenetics. Women with PCOS are in increased risk of developing endometrial, ovarian and breast cancer. This study will highlight the probable risk factors of developing PCOS, the interplay of harmones and its possible association in developing cancer.

ETIOLOGY AND RISK FACTORS CONTRIBUTING TO PCOS[2]

I. External factors
II. Internal factors.

A table on etiology and risk factors contributing to pcos summarized in Table no.1.

EXTERNAL FACTORS	INTERNAL FACTORS
1. Epigenetics	1. Insulin resistance
2. Environmental factors	2. Hyperandrogenism
3. Physical and emotional stress	3. Inflammation
4. Diet	4. Oxidative stress
	5. Obesity

A. EXTERNAL FACTORS

1. Epigenetics

Refers to inheritable alterations in genome and gene expression without any changes in DNA sequence. These changes involve adding or omitting chemical components on DNA or histone. Increased Lutenising harmone activity is a seen phenomenon in PCOS women. It may lead to problems in follicle development and hyperandrogenism, common among patients of PCOS.

2. Enivornmental toxins

EDC(endocrine disrupting chemicals) are exogenous agent that interferes with the synthesis, secretion, transport, binding, action or elimination of natural harmones in the body that are

responsible for the maintenance of homeostasis, reproduction, development and behaviour.[7] EDCs may act as harmone agonists or antagonists in binding to their receptors.[8] Their structure imitates steroid harmone actions.[9]

Prolonged and continuous exposure to EDCs from prenatal to adolescence can cause suspectibility to PCOS.[9,10]

3. Physical and Emotional stress

Chronic stress results in hypertrophy and hyperplasia of adipocytes. Also it is responsible for making an inflammatory condition by leading to high levels of inflammatory cytokines like IL-6 (interleukin-6) and TNF-alpha (tumour necrotising factor) along with disrupting oxidant-antioxidant balance.[11] It also plays a vital role in insulin resistance.

Stress triggers HPA axis(hypothalamic-pituitary –adrenal axis) to release cortisol. Cortisol leads to insulin resistance by stimulating visceral fat accumulation, gluconeogenesis and lipolysis.[13] other stress may refer to inference with anti-mullerian harmone (AMH) and changing sex harmone levels.[12,13]

4. Diet

Saturated fatty acids (SFAs) plays a role in PCOS by producing an inflammatory status[14] and reducing insulin sensitivity. Saturated fatty acids induces inflammation by triggering an increase in TNF-alpha level in circulation.

Vitamin-D may exacerbate PCOS[15,16] or the comorbidities induced by PCOS. Vitamin –D deficiency may result in insulin resistance by causing inflammatory response.[15,17]

B. INTERNAL FACTORS

1. Insulin resistance

Insulin resistance is independent of patient's adiposity, body fat topography and androgen levels.[18,19] Insulin directly triggers androgen production in ovarian theca cells and grow.[21] And also influence on adipose tissue and inflammation.

2. Hyperandrogenism

Hyperandrogenism (HA) reduces SHBG level, leading to a high concentration of free testosterone.[18,20] Its observed that PCOS women with higher concentration of free testosterone in plasma which converts estrone in adipose tissue. Increased alteration of

estrone to estradiol affect follicle growth and increases the LH to FSH ratio causing ovulatory dysfunction. HA can result in AMH upregulation which inhibits ovulation and development of follicles by different mechanism. It also influences insulin resistance, inflammation and oxidative stress.

3. Inflammation

Appropriate inflammation is a vital cause of oocyte growth and ovulation.[22] high levels of white blood cells, C-reactive protein and other inflammatory biomarkers in peripheral blood are associated with PCOS. Inflammation is a cause for hyperandrogenism. TNF-alpha is a pro-inflammatory chemicals which worsens insulin resistance. Increase in C-reactive protein is another cause for insulin resistance.

4. Oxidative stress

Is an imbalance between pro-oxidants and antioxidants.[23] Overproduction of oxidative chemicals cause various damage to vital molecules such as lipids, proteins and DNA. Oxidative stress also imposes a major effect on obesity.[23]

5. Obesity

It's a key in low grade inflammation.[24] Accumulation of adipocytes in visceral fat leads to hypoxia and consequent necrosis which causes inflammatory cytokines production. Adipocyte death due to hypertrophy causes and inflammatory state. Excess abdominal fat is also responsible for inflammatory condition. Obesity also plays a role in hyperinsulinemia, insulin resistance and hyperandrogenism occurrence.

A summary of most representative molecular mechanisms of PCOS pathogenesis id presented in Figure 1.

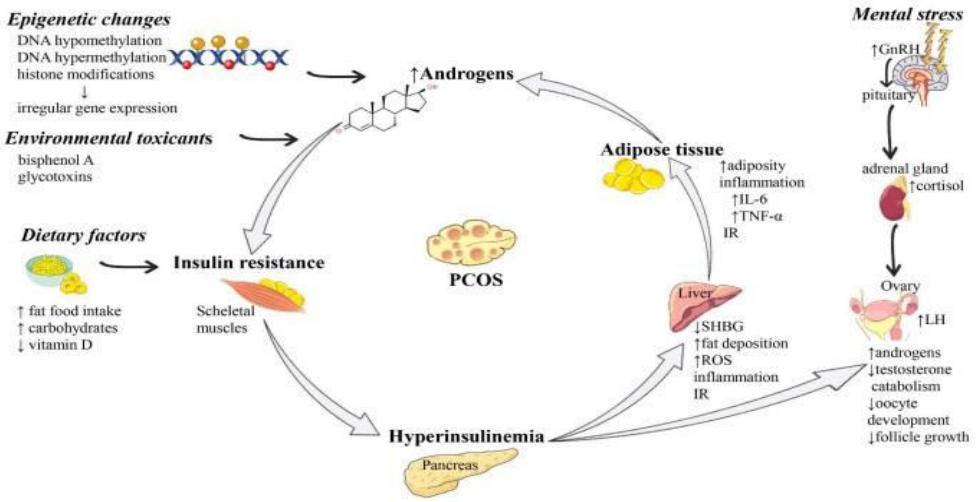
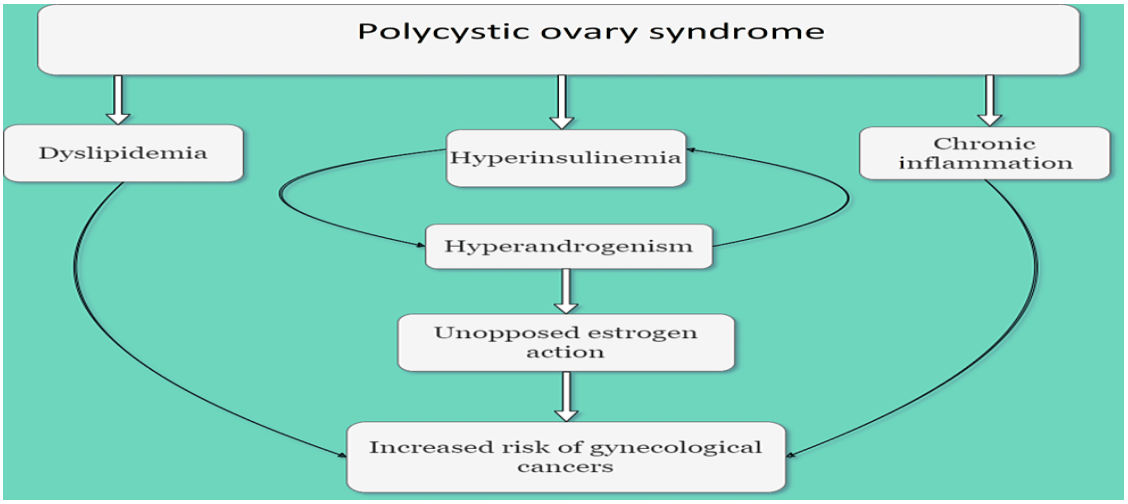


Figure 1: Summarized scheme regarding patho-physiology of PCOS.

CLINICAL MANIFESTATIONS

- Menstrual dysfunction[3]: Oligomenorrhea (few menstrual periods) or amenorrhea (no menstrual periods).
- Infertility[3]: due to chronic anovulation
- Hirsutism & Acne vulgaris[3]: due to high levels of androgen.
- Androgenic alopecia
- Obesity[3]- insulin resistance, hyperandrogenism
- Acanthosis nigricans[3]
- Insulin resistance & diabetes mellitus[3] – metabolic malfunctioning signs

RELATION BETWEEN ETIOLOGIES THAT EXPLAINS PCOS AND ITS CANCER RISK



PCOS AND ITS ROLE IN DEVELOPMENT OF ENDOMETRIAL CARCINOMA[26]

- Major factor involves **CHRONIC HORMONAL STIMULATION**.
- "Unopposed estrogen hypothesis"- exposure to endogenous/exogenous oestrogen – results in mitotic activity of endometrium -- endometrial hyperplasia---endometrial cancer.
- High oestrogen and progesterone – anovulation – failure of endometrial shedding --- endometrial cancer.[26]
- Hyperinsulinemia –caused by insulin resistance–promotes endometrial cell proliferation– endometrial cancer.
- Hypersecretion of Lutenising harmone(LH)- anovulatory Cycles – endometrial hyperplasia – endometrial cancer.[26]
- Metabolic syndrome–triad of obesity, hyperinsulinemia and diabetes – endometrial cancer pathogens.

PCOS AND ITS ROLE IN DEVELOPMENT OF OVARIAN CANCER[26]

- Gene mutations –abnormal protein formation—initiation of cell metastasis – ovarian cancer.
- Hyperandrogenism – testosterone enchances proliferation of epithelial cells in ovary - in ovarian stromal cells with abnormal cell morphology – ovarian cancer.[26]
- EDC(enivornmental disrupting chemicals) –act as steroid harmones (estrogen & progesterone)- triggers pro-inflammatory pathway & oxidative stress-- increased angiogenesis –ovarian cancer.
- EDC- creates oxidative stress – induce inflammatory immune cells – triggers steroidogenesis & DNA damage---ovarian cancer.[26]

PCOS AND ITS ROLE IN DEVELOPMENT OF BREAST CANCER[26]

- Increased levels of androgen –act on epithelial cells of breast –abnormal cell morphology- Breast cancer.
- Hyperinsulinemia – Breast cancer.

PCOS AS PUSHPAGNI JATAHARINI

Exact description of PCOS is not found in Ayurvedic classics rather symptoms are close to the Pushpaghni Jataharini[6] as described by Acharya Kashyapa. In this jataharini[6], Vritha Pushpam (**anovulation**), Yathakalam Prapashyati (i.e. **menstruation occurs at regular**

interval), Sthula Ganda (a feature of **obesity**), Lomasha Ganda (i.e., **hair present on face; hyperandrogenism**) are found.

PREVENTION OF PCOD

A. Lifestyle modifications and non-pharmacological approaches.[2]

- ✓ Weight loss
- ✓ Diet
- ✓ Exercise

B. Alternative medicine[2]

- ✓ Acupuncture
- ✓ Diet therapy
- ✓ Immuno therapy
- ✓ Pyschotherapy

C. Pharmocological therapy.[2]

CONCLUSION

Polycystic ovary syndrome (PCOS) affects 4% to 18% of reproductive-aged women and is associated with reproductive, metabolic and psychological dysfunction. Its a complex disease and the **central mechanism** is difficult to understand & state.

PCOS affects quality of life and can worsen anxiety and depression either due to the features of PCOS or due to the diagnosis of a chronic disease. No treatment can be claimed as a magic bullet as it targets the clinical symptoms rather than curing the syndrome.

Current studies suggests that women of all ages with PCOS are at an **increased risk of developing cancer** relating to reproductive organs on a long term exposure. Lifestyle interventions like **dietary intake, eating behaviour, physical activity levels, and quality of life** should be recommended in all women with PCOS. **Proper counselling** has to be done to the women with PCOS, stating the risk of cancer on a long go.

An appropriately **designed diet** regimen for a PCOS patient is one that not only aims at weight management, but also prevents the long-term risks of PCOS- Type II Diabetes, cardiovascular diseases etc. The diet should be such that not only the **insulin levels gets reduced**, the insulin sensitivity is also improved as insulin resistance and hyperinsulinaemia

are the key aetiological factors of PCOS. Hence a **high fiber, low saturated fat** and **low glycaemic index carbohydrate diet** is strongly recommended.

Weight loss is the most essential part of treatment, as it rectifies hormonal imbalance, elevates the insulin and sex hormone binding globulin levels and reduces the testosterone levels. Several Yoga postures aid in weight loss, relieve stress and improve the ovarian blood supply, thereby assisting treatment of PCOS. Different Asanas like **Sarvangasana, Ardhamatsyendrasana, Mandukasana, Suryanamaskara** and Pranayama like **Kapalabhati, Ujjayi, Anuloma-Viloma Pranayama** can be very beneficial for PCOS patients.

Adopting holistic treatment of Ayurveda-proper lifestyle with appropriately balanced diet, yoga and pranayama can prove to be a wholesome and effective management protocol for PCOS. **Ayurvedic treatment** strengthen and revitalize the female reproductive system, regularize menstrual cycles, rectify hormonal imbalances; thus enabling women to lead a healthy life.

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