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It gives me great joy to bring you the 3rd volume of our ReproGenQ newsletter which is focused on Polycystic Ovary Syndrome (PCOS). I am delighted to let you know that ReproGenQ newsletter represented by the Indian Fertility Society which is always bring attention on fertility issue of our society. The PCOS is the single most common neuroendocrine disorder which affects between 5 to 15% of reproductive-aged women depending on diagnostic criteria. We have some excellent articles in this volume from our own members as well as from other senior scientists on a subject not discussed before, but definitely needs attention. Attention towards management of the most distressing features of PCOS is most important during early phase of puberty when most dynamic hormonal changes occur in female reproductive system. Additional research in diagnosis and treatment approaches is needed for this complex neuroendocrine disorder. This newsletter is not only the platform to celebrate our success and acknowledge our well renowned scientists/colleagues for their great scientific contribution to human society but also a medium to understand overall team work of our small family.

On behalf of the editorial team, I thank you for your continued support of ReproGenQ newsletter. I must thank our academic partner as well as event sponsor inDNA Life Sciences Pvt. Ltd for their financial support to this Newsletter.

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Polycystic Ovary Syndrome and Type 2 Diabetes Mellitus

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Current and future status of Polycystic ovary syndrome (PCOS)

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Bisphenol A and PCOS: Does the link exist?

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POLYCYSTIC OVARY SYNDROME AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by ovulatory dysfunction and hyperandrogenism. PCOS is the most common endocrinopathy of reproductive-age women and the consequences of PCOS extend beyond the reproductive axis. There are multiple diagnostic criteria systems for PCOS which include abnormal menstruation, clinical signs and/or biochemical evidence of high androgen levels and polycystic ovaries seen on an ultrasound. Estimates of PCOS prevalence vary widely. It’s reported to affect anywhere from 2.2 to 26 percent of women worldwide. Most women with PCOS have insulin resistance and compensatory hyperinsulinemia. This is suggested to be due to intrinsic insulin resistance mechanisms.

INTRODUCTION:

Most women with PCOS, particularly those presenting with overweight or obesity, have insulin resistance and compensatory hyperinsulinemia which is partly attributed to intrinsic insulin resistance mechanisms.1 PCOS and type 2 diabetes mellitus (T2DM) are both associated with insulin resistance.

INTERSECTION OF PCOS AND TYPE 2 DIABETES MELLITUS

The pathogenesis of T2DM involves a combination of insulin resistance and relative impairment of insulin secretion leading to hyperglycemia and is often accompanied by hypertension and dyslipidemia. Insulin resistance is present in 65%–80% of women with PCOS and plays a significant role in its etiology. Insulin directly causes specialized cells in the ovary called theca cells to be produce the androgens. Insulin can also trigger an increase in the actual number of theca cells within the ovary. High levels of insulin can also decrease the production of sex hormone binding globulin (SHBG) which further leads to high levels of androgens. PCOS is an independent risk factor for development of T2DM. A study conducted in USA revealed PCOS was associated with two-fold higher odds of incident diabetes (adjusted OR 2.4). A study on Danish women found that those with PCOS were four times as likely to develop T2DM as non-PCOS women. We also showed high prevalence (36.3%) of abnormal glucose tolerance (AGT) among young Indian women with PCOS.1 We studied a total of 2,014 women with PCOS diagnosed on the basis of the Rotterdam 2003 criteria were enrolled, and the data of 1,746 subjects were analyzed. In addition to recording clinical, biochemical, and hormone parameters, a 75 g OGTT was administered. The mean age of the subjects was 23.8 ± 5.3 years, with a mean BMI of 24.9 ± 4.4 kg/m2. The overall prevalence of AGT was 36.3% (6.3% diabetes and 30% impaired fasting plasma glucose/impaired glucose tolerance) using American Diabetes Association criteria. The glucose intolerance showed a rising trend with advancing age (30.3%, 35.4%, 51%, and 58.8% in the second, third, fourth, and fifth decades, respectively) and increasing BMI. Family history of diabetes mellitus was present in 54.6% (953/1,746) subjects, and it did not correlate with any of the studied parameters except waist circumference and BMI. Sensitivity was better with 2-hour post-OGTT glucose values as compared with fasting plasma glucose, since using fasting plasma glucose alone would have missed the diagnosis in 107 (6.1%) subjects.

We conclude that AGT is high among young Indian women with PCOS and that it is not predicted by family history of type 2 DM. OGTT significantly improves the detection rate of AGT among Indian women with PCOS.

Conversely women with T2DM have shown to have high evidence of PCO morphology.1 We studied one hundred and five reproductive age group women with diet and/or oral hypoglycemic treated T2DM were the subjects of the study. Sixty age-matched non-diabetic women served as controls. Transabdominal ultrasonographic assessment of the ovaries was used to diagnose PCO. Clinical biochemical and hormonal parameters were also noted. We found Ultrasonographic prevalence of PCO was higher in women with diabetes than in non-diabetic subjects (61.0% vs 36.7%, P < 0.003) whereas that of PCOS was 37.1% in diabetic subjects and 25% in non-diabetic controls (P > 0.1). Diabetic women with PCO had diabetes of significantly longer duration than those without PCO (4.19±2.0 versus 2.9±1.6 yrs; p < 0.05). Among both diabetic and non-diabetic women, those with PCO had significantly higher plasma LH, LH/FSH ratio, total testosterone and androstenedione levels.

LONGITUDINAL Trajectory of PCOS and T2DM

There are suggestions that prevalence of this disorder seems to run parallel to the epidemic of T2DM in India. Women with PCOS tend to be diagnosed with diabetes four years earlier than women without PCOS. A recent longitudinal study revealed that obesity and abdominal fat distribution, but not hyperandrogenism per se, in women with PCOS in the mid-fertile years were the major risk factors for DM2 development.4 Approximately 27% of premenopausal women with T2DM also have
PCOS. Pregnant women with PCOS are nearly three times as likely as women without it to develop gestational diabetes which in turn can cause birth complications such as premature birth, jaundice, breathing issues, and more.

COMMON PREVENTIVE STRATEGIES

Lifestyle changes help with reducing insulin levels and improving symptoms like weight gain, hair growth and acne. A research study compared a moderately low carb diet with a standard low-fat diet. The results showed that low carb diet conclusively improve insulin, cholesterol and testosterone levels compared with low fat diet.

Thus, PCOS is a syndrome beyond menstrual irregularity and infertility with long-term metabolic consequences and hence, there is a need for initiatives at all levels to tackle this epidemic.

REFERENCES


Genetic elements associated with PCOS

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects reproductive-age women. The worldwide prevalence of this endocrine disorder is 5-10% and it is multifactorial diseases that cause infertility and lead to social imbalance. Based on the observed phenotypes PCOS is classified into phenotype A, phenotype B, phenotype C and phenotype D. Phenotype A and B are classic phenotypes having high insulin resistance, metabolic and increased menstrual dysfunction. Increased Anti-Müllerian hormone (AMH) level is also the characteristics of A and B phenotypes. Phenotype C (ovulatory PCOS) individuals show high hirsutism score and less elevated insulin levels and also androgen and atherogenic lipids level is high as compared to the other PCOS phenotype. Non-hyperandrogenic or phenotype D is characterized by the average androgen level, regular menstrual cycle with irregularities and a lower ratio of LH/FSH and T3 and T4 hormones as compared to the classic phenotype. Intrinsic activation of the theca cell in the absence of the trophic factors leads to increased secretion of the androgen commonly seen in the PCOS patients. Alteration in the insulin gene expression pathways, glyco-oxidative pathways also underlying in the pathology of the PCOS. This pathology is not easy to diagnose due to the overlapping symptoms. Menstrual dysfunction, infertility, hirsutism, metabolic syndrome and obesity are the clinical symptoms of PCOS. A single test cannot easily detect PCOS due to the complex and multifactorial nature. PCOS is diagnosed with ovulatory dysfunction, hyperandrogenism (HA) and polycystic ovarian morphology (PCOM) on ultrasound. Derangement of insulin secretion and androgen synthesis, ovulatory dysfunction, the balance of the pro and antioxidants system, gonadotrophin ratio, are associated with the PCOS. Glucose intolerance, diabetes mellitus type 2 (T2DM), hypertension, dyslipidemia, hepatic steatosis are the metabolic disorders that are related to the PCOS. PCOS is a heterogeneous disorder resulting from multiple gene interactions along with environmental factors and an X-linked polygenic disorder. Many studies had done to understand the genetics of the PCOS cause, but no single marker has emerged as a convincing biomarker for the cause of PCOS. Four main factors contributing to various degrees in PCOS are insulin resistance, an increase in ovarian adrenal and ovarian androgen synthesis, partial folliculogenesis arrest and dysfunction of neuroendocrine axis. Genes that associated with development and progression of the PCOS pathology includes ovarian and adrenal steroidogenesis, action and effects of GnRH, effects of sex steroid and gene that regulate the activity of insulin. Identifying the genetic variants that cause PCOS will help us to understand the multifactorial nature and genetic architecture of this disease.

INTRODUCTION:

Gene/mutations that directly or indirectly affect the functioning of the ovary are associated with the PCOS. Genes involved in the ovarian and adrenal steroidogenesis, gonadotrophin action and regulation, insulin action and secretion are associated with PCOS. There are also other genes and the epigenetics related to the development of PCOS. An elevated level of the androgen is one of common disorder that is related to the PCOS. There are multiple androgen sources, but the ovary and adrenal gland are the primary androgen sources in PCOS. The elevated levels of the androgen and enzyme required for the androgen synthesis observed in the hyperandrogenic women. The intrinsic dysregulation in the biosynthesis of the steroids in the theca cells leads to the increased androgen level in PCOS. There is numerous gene related to the elevation of the androgen level and underlying causes for PCOS development.

KEY GENES ASSOCIATED WITH PCOS:

The CYP genes are mainly involved in ovarian and adrenal steroidogenesis. CYP genes that are associated with HA pathology includes CYP11A (cytochrome P450 side-chain cleavage enzyme gene), CYP21, CYP17 (cytochrome P450 17-hydroxylase/17, 20-desmolase gene), and CYP19 (aromatase). Variation and polymorphism in the gene CYP11A are associated with PCOS. If P450 determines the rate-limiting step in converting the cholesterol to the progesterone. ¹ Repetition of the (TTTTA) sequence in the 5’ UTR region of CYP11A locus is associated with the PCOS development. The polymorphism in these six repeats (TTTTA) is involved in the increased level of the progesterone in the PCOS women. CYP19 (aromatase) is vital for estrogen synthesis. It is essential for the conversion of the androgen to estrogen. Intronic variant rs2414096 of CYP19 is related to the development of the PCOS. ² Lower activity of the CYP19 reported in PCOS. ² CYP21 variations lead to the ineffective steroidogenesis that leads to PCOS. ³ CYP17 is a critical enzyme in the steroid synthesis. CYP17 gene encodes a cytochrome P450 enzyme and is involved in 17-hydroxylase activity. This enzyme required for the conversion of the progesterone into 17-hydroxyprogesterone and pregnenolone into 17-hydroxypregnenolone. The 17,20-lyase activity of the cytochrome P450 is required to convert 17-hydroxypregnenolone into dehydroepiandrosterone (DHEA) and 4-androstenedione. Increased DHEA and DHEAS are found in the women with PCOS and make this gene a potential candidate linked with PCOS. Polymorphism at promoter level of CYP17 gene and increased expression of CYP17 associated with elevated levels of androgen in HA and PCOS. ⁴ Steroidogenic enzyme similar to theca cell in the formation of the DHEA in the Initiating step considered in the androgen biosynthesis is transporting the cholesterol via STAR gene (steroidogenic acute regulatory protein) from outer to the inner mitochondrial membrane. Variations between the exon 5 and 7 of the STAR gene play a critical role in
the PCOS occurrence. High level of StAR protein found in the PCOS individual. Androgen receptor (AR) encoded by the AR gene present on the X chromosomes plays a vital role in developing the male characteristics features. The N terminal activation region of the AR gene contains a CAG repeats, and the length of the CAG repeats it is also now considered one of contributing factor for PCOS. Studies also showed that the antagonist of AR (flutamide) restores the GnRH pulse generator's sensitivity and recover ovulation and menstruation. Androgen receptor (AR) gene mutations also related to PCOS. 

Biosynthesis of the testosterone assisted by HSD17B5 gene encodes enzyme17 β-hydroxysteroid dehydrogenase type 5 in the adrenal gland and theca cell. Testosterone levels is affected due to polymorphism at the intronic region rs1937845 of HSD17B5 gene and increased the risk of developing PCOS. Sex Hormone Binding Globulin Gene (SHBG) interacts with the estrogens and testosterone and regulate the levels of the sex hormone. Therefore, the bioactive concentration of the sex hormone is regulated by SHBG. Single nucleotide polymorphism in the SHBG gene also associated with the PCOS. At the transcription start site of SHBG two related transcription factor (HNF-α and COUP-TF1) compete for binding and regulate the promoter activity of the SHBG gene. Binding of the HNF-α increases the promoter activity while the COUP-TF1 decrease the promoter activity of SHBG. Binding of the COUP-TF1 near the transcription start site of the SHBG leads the elevated level of free plasma testosterone associated with HA pathology and contributes to PCOS development. These two gene AR and SHBG plays an essential role in the effects of steroid hormone, and there malfunctioning contribute to the development of PCOS. Progesterone provides a negative feedback mechanism in controlling the GnRH pulse frequency. Elevation in androgen levels reduced this feedback mechanism and resulted in increased pulse frequency of the GnRH in PCOS. Alterations in GnRH frequency lead to an increase in the LH level and reduced FSH level. PCOS individuals’ ovaries show hypersensitivity towards the LH and escape LH receptor downregulation contributing to PCOS development. A point mutation in the gene encodes the β subunits of the LH related to PCOS. In female anti-Mullerian hormone (AMH) is the regulator of the folliculogenesis. Variations in the AMH gene is also one of the contributing factors of the PCOS. Follicle-stimulating hormone receptor (FSH-R) gene encodes G-protein-coupled receptor, which vital for the development of gonads. Disruption in the structure and function of the FSH-R gene leads to the hormonal imbalance causes PCOS. Disruption and mutations of LH, LHR, AMH and FSHR genes lead to abnormal secretion of the GnRH that is one of the main contributing factors of PCOS. Insulin plays an essential role in producing the androgen through insulin receptors present on the theca cells. Insulin resistance (IR) is one of the hallmarks of the PCOS. Around 50% to 90% of women with PCOS have IR. HA inhibits the insulin degradation by liver cells, causes the reduction in the expression andsensitivity of the Glu 4 transporter, contributes in central obesity that aggravates IR which is associated with the development and occurrence of the PCOS. Studies have also shown that polymorphism of a variable number of the tandem repeat (VNTR) present at the 5’ untranslated region of the INS gene linked with the PCOS. To find the association of the INSR (insulin receptor) and PCOS large part of chromosome 19 searched and found that D19S584 (a region where INSR gene is present) is strongly associated with PCOS. Binding of the insulin to its high-affinity INSR leads to the activation of the receptors that cause the phosphorylation of the second messenger protein IRS-1 (insulin receptor substrate protein-1) and IRS-2 (insulin receptor substrate protein-2). Activated IRS protein stimulate the transport of the glucose by translocation of the GLUT4 from the cytoplasm to the plasma membrane via PI3k and Akt pathways and play important role glucose metabolism. Various studies also showed higher frequency of Arg972 in IRS-1 in PCOS patients. ENPP1 gene product ectonucleotide pyrophosphate/phosphodiesterase interacts with the INSR and play important role in the insulin signalling. Studies reported the overexpression of the ENPP1 in PCOS. CAPN10 gene encodes calcium dependent protease that participates in the insulin secretion and action. Thus malfunctioning of the CAPN10 expression are found to be a contributor of the IR that is one of the main factor for the development of the PCOS. Other gene which are linked with the PCOS is FTO and SRD5A1. Single nucleotide polymorphism rs9939609 in FTO (Fat mass obesity) gene is associated with T2DM and obesity linked with the PCOS. Variants of the SRD5A1 gene are also reported to increase the risk of hirsutism and linked with PCOS. Epigenetics changes are also associated with the occurrence and progression of the many pathologies such as cancer, T2DM, PCOS. Methylation of CPG island in PPARG1, NCOA1 are linked to ovarian dysfunction and at the high risk of PCOS development.

CONCLUSION

PCOS is one of the complex and multifactorial pathologies that affects most women at the reproductive age. Many gene association studies were going and carried out to understand the exact nature and architecture of the genetic element involved in the PCOS. In recent years, gene-wide association studies shed light on the various genes associated with PCOS development. These studies found new loci that are associated with PCOS development. Gene associated with loci is TOX3, RAB8B, SUX5, HMG2A, C9orf13, SUMO1p1, YAP1, INSR. Association of the gene that affects the synthesis of the androgen, insulin secretion and action, gene that affects the activity and regulation of the gonadotrophins found with other pathology (HA, IR) linked with PCOS progression and occurrence. The other recent gene that are associated with the development of the PCOS are: RAD50, FSHB, ERBB4, THADA, KR1. Cytochrome P450 family gene plays a vital role in the androgen biosynthesis, alteration in their expression develops hyperandrogenism that exacerbates PCOS. LH, LHR, FSHR and AMH are involved in the regulation of GnRH, dysregulations of these genes lead to the hormonal imbalance that is a contributor to PCOS development. SHBG and AR play important role in mediating the effect of the androgen an thus potential candidate in PCOS. Polymorphism in the different genes involved in insulin secretion and androgen biosynthesis reported increasing PCOS development risk. PCOS etiology is still not clearly understood, and there is yet no cure for this pathology. All gene associated studies understand that the all the genetic factor affect the ovarian androgen activity and metabolic dysfunction. Finding the genetic element underlying the various pathology linked with PCOS helps to elucidate a single genetic marker responsible for developing PCOS and developing medical interventions that could cure or prevent the progression and development of PCOS.

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CURRENT AND FUTURE STATUS OF POLYCYSTIC OVARY SYNDROME (PCOS)—AN INDIAN PERSPECTIVE

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ABSTRACT

Polycystic ovarian disease is a global threat to women of reproductive age which ranges from 18-45 years of age. Women with such syndrome face a lot of challenges like irregular or scanty periods during menstruation, depression, obesity, facial hair, and inability to conceive. If it is not controlled it can lead to heart disease, obesity, and diabetes. In India, there is a high incidence of PCOD that severely affects young women. Late diagnosis due to lack of awareness is one of the chief factors that this disease is spreading at a faster pace. This disease cannot be cured but can be very well controlled by spreading awareness among women. A balanced diet, a lot of exercise, a well-managed lifestyle, and awareness about this menace can help to eradicate this dreadful syndrome.

INTRODUCTION

PCOD (Polycystic Ovarian Disease) is a global issue that has affected women throughout the world. In India, PCOD is the major ailment that has engulfed younger women. The average age group affected by PCOD is 18-45 years.¹ There is about 5-10% of women are facing this menace globally and in India, one out of every ten women are facing PCOS. Even in the present scenario people are not aware of this medical condition which leads to late diagnosis.³

INCIDENCE OF PCOS IN INDIA

AIIMS has conducted a study that shows about 20-25 percent of Indian women of reproductive age are suffering from PCOS. In this study it was observed that 35-50% of women were having a fatty liver, 70% were insulin resistant and 60% were obese.³ Its severity and symptoms are not properly understood. It has been observed that the insulin level is also higher in women suffering from PCOS.

In a nationwide survey conducted by ICMR (Indian Council of Medical Research) it was shown that PCOS has shown a great rise among teenage girls and women. It has been observed that the insulin level is also higher in women suffering from PCOS. Androgens like testosterone are produced in larger amounts in PCOS patients due to high insulin production. It is harder to lose weight among women with PCOS due to insulin resistance.³ If the condition remains unchecked and undiagnosed it can result in infertility among women along with other health conditions.

SYMPTOMS ASSOCIATED WITH PCOS

There are several symptoms associated with this condition like higher BMI, fatigue, unwanted hair growth, infertility, pelvic pain, headaches, sleep problems, mood swings, and higher levels of testosterone and polycystic ovaries.³ Young girls suffer from scanty and irregular periods. It’s a familial condition that means it runs among families, from mother to daughter, etc. Oligomenorrhea, amenorrhea, and prolonged erratic menstrual flow are common symptoms observed. Women with PCOS suffer from other health conditions too like sleep apnoea, high blood pressure, high thyroid levels, high cholesterol, and depression. They are more likely to develop endometrial, ovarian, and Breast cancer.³

When there are primary defects in the hypothalamic-pituitary axis then it leads to abnormal insulin secretion and action which finally leads to disrupted ovarian function. Though the actual reason for PCOS is not known it has been linked to obesity and insulin resistance. It has been studied that insulin regulates ovarian function, and when insulin is produced in excess amounts it leads to the production of androgens in large amounts that lead to anovulation.

PCOS also leads to hormonal imbalances which include an increase in luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) levels whereas there is a decrease in follicular-stimulating hormone (FSH) levels. High levels of GnRH lead to an increase in androgens. Prolactin levels are also high in 25% of patients with PCOS.³ Therapeutic interventions include controlling sex hormone-binding globulin (SHBG) levels, regulation of insulin and androgen levels. Alteration of thecal cells leads to the normal production of testosterone, progesterone, and 17-hydroxyprogesterone.³

CONCLUSION

Though we cannot eradicate this menace from its roots its symptoms are manageable. It is very important to make women aware of this disease so that it can be diagnosed at an early age and taken care of. Yoga, exercise, intake of water, balanced diet are many factors that can help in controlling PCOD to a larger extent. In India, women are facing a lot of social suppressions due to this syndrome and its incidence is increasing day by day. The purpose of this study is to spread awareness at the grass root level.

Future Perspectives: PCOS is a condition that cannot be cured but can be managed by controlling symptoms. If the women avoid using junk diet, do yoga and exercise regularly and change their lifestyle, it is possible to control and manage the symptoms to a larger extent. A high fiber diet that includes cauliflower, green and red peppers, beans and lentils, tomatoes, spinach, and a diet rich in 3-omega fatty acids can be beneficial in PCOS. Losing weight will help to control the menstrual cycle and hormonal imbalance. Diet control, exercise, yoga, and a healthy lifestyle can help to manage PCOS.
lifestyle can prove to be a boon in controlling symptoms of PCOS that can help the women suffering from this condition to a larger extent. It's very important to spread awareness among women regarding this dreaded condition for beneficial results.

REFERENCES


**BISPHENOL AND PCOS: DOES THE LINK EXIST?**

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**ABSTRACT**

Endocrine disrupting agents (EDAs) are natural or synthetic compounds that usually interfere with the endocrine system by mimicking or antagonizing endogenous steroid hormones. Bisphenol-A (BPA) is one of the EDAs that is widely used in the manufacture of plastic products. BPA has estrogenic activity and can bind to α- and β-estrogen receptors (ER) both in vivo and in vitro. The detection level of BPA has been found in almost all human body fluids, including follicular fluid. BPA concentrations are higher in women with polycystic ovarian syndrome (PCOS) than in reproductively healthy women, but the path of causality has not been identified. It has been suggested that environmental exposure to nutritional, chemical or physical factors may alter gene expression and changes the epigenome that can modify adult disease susceptibility including PCOS.

**INTRODUCTION**

EDAs can adversely affect hormone balance by disrupting the secretion or regulation of hormones. BPA is 4,4’-dihydroxy-2,2-diphenyl propane and was first synthesized in 1891 1. It has been widely used in the manufacture of polycarbonate and epoxy resins which are commonly used for food and beverage storage containers, detergents, soaps, shampoos, nail paints etc. 2. BPA is now considered as a widespread environmental pollutant and exposure of BPA in human is continuous.

Found ubiquitously in the environment, BPA is absorbed via ingestion, inhalation and dermal routes 3. The safe exposure level of BPA in humans is <50 μg/kg/day 4. The biological half-life of BPA is approximately 6 h BPA and gets completely excreted via urine in 24 h. BPA is mainly metabolized by the hepatic glucuronidation pathway 5. Despite this rapid metabolism, BPA can remain accumulated in tissues for longer duration and undergoes a conjugation-deconjugation cycling that may delay its excretion 6. BPA gets accumulated in reproductive organs and can exert its impact at a very low dose. BPA has estrogenic activity and can bind to α- and β-estrogen receptors (ER) both in vivo and in vitro 7. It can exert estrogenic effects at 2 μg/kg 8.

The detection level of BPA has been found in almost all human body fluids, including follicular fluid 9. It has been suggested that oocytes are also exposed to BPA during the folliculogenesis process 10. Various studies have shown the adverse effects BPA on the maturing oocyte 11. During in vitro fertilization (IVF) treatment, negative correlation was found between urinary BPA concentrations, oocytes quality, and number of oocytes retrieved 12. These findings raised concerns that environmental BPA exposure may cause the decline of ovarian reserve and fertility in women 13. BPA toxicity during the perinatal phase even at concentrations comparable to normal levels of human exposure significantly disrupts ovarian and reproductive activity in females in animal models 14.

**BPA AND PCOS**

BPA regulates pathways involving cell replication, differentiation, and apoptosis such as STAT3, PI3K/AKT, and MAPK pathways 15. BPA may also interfere with natural metabolic function as have obesogenic properties thereby predisposing the body to obesity.

PCOS is a multifactorial metabolic-endocrine disorder usually present with different phenotypes in women of reproductive age. The diagnosis of PCOS is based on at least two of the three criteria: (1) clinical hyperandrogenism (with hirsutism, acne, seborrhea and alopecia) and/or biochemical hyperandrogenism (increased circulating androgens levels); (2) presence of ovarian cysts assessed by ultrasound examination and (3) oligo-amenorrhea with oligoanovulation.

Studies have found an association of BPA with the PCOS 16. BPA concentrations are higher in PCOS women than in reproductively healthy women 17. Various studies have found that BPA is associated with obesity, changes in puberty onset and ovulatory dysfunction 18. Neonatal rats exposed to BPA were found to have PCOS like phenotype and insulin insensitivity. Rat ovarian theca interstitial cell was culture with BPA induced increased testosterone synthesis 19,20. It was suggested that this may be because of the enhanced expression of mRNA of enzymes involved in the androgen synthesis 21,22. It was also found in a study that both lean and overweight PCOS patients had a high level of BPA in comparison to lean and overweight controls. This study also revealed a positive correlation between BPA and insulin resistance.

Few studies have shown that female gonads are affected by BPA which leads to pathophysiological changes in gonads leading to reproductive and endocrinological abnormality 23,24. BPA interferes with steriodogenesis, folliculogenesis, and ovarian morphology 25. There are evidence indicating the existence of a bidirectional interaction between BPA and androgens. Androgens interfere with BPA clearance in the liver leading to increased serum levels of BPA 26. BPA also alters androgen metabolism in liver. It acts as a potent SHBG binder thereby displacing androgens resulting in increased levels of serum-free androgens 27. It has been reported that uridine diphosphoglucuronosyl transferase activity (UDGT), a liver enzyme involved in BPA clearance from the circulation, is down-regulated by androgens 28.

It has also been reported that BPA significantly inhibited the activity of two different testosterone hydroxylases (2-and 6-hydroxylase), leading to decreased testosterone catabolism and therefore increased testosterone concentrations 29. PCOS ovarian hyperandrogenism is suggested to be because of partial activation of the steriodigenic
The mechanisms were attributed to increased mRNA expression of the enzymes involved in steroid production pathways such as 17α hydroxylase, cholesterol side chain cleavage enzyme, and steroidogenic acute regulatory protein.

It has already shown that serum BPA levels were higher in Caucasian PCOS patients, in non-PCOS obese patients and in non-PCOS insulin-resistant patients. This further helped in hypothesizing that BPA might be involved in the insulin resistance of PCOS. BPA promotes an inflammatory response and direct action on adipocytes and macrophages infiltrating the adipose tissue. It has been shown already that chronic inflammation leads to insulin resistance and compensatory hyperinsulinemia. This in turn leads to development of the typical increased amplitude and frequency of GnRH and LH pulse secretion as seen in PCOS. Figure 1 shows the suggested mechanisms of BPA induced changes that might be associated with development of PCOS.

**BPA induced genetic and epigenetic changes**

It is a known fact that environmental exposure to nutritional, chemical or physical factors may alter gene expression and changes the epigenome that can modify adult disease susceptibility. BPA can also affect gene expression directly and/or to impact epigenetic modification of fertility-related genes. The epigenetic modulation of gene expression has also been investigated as a possible target of environmental toxins, including oestrogenic chemicals.

There are evidences indicating that epigenetic alterations, including aberrant DNA methylation might contribute to the development of PCOS. Specific genes such as LHR, EPHX1, and CYP19A1 associated with PCOS showed aberrant DNA methylation in distinct tissues. In a recent study, 92 differentially expressed genes unique to PCOS granulosa cells were identified in comparison with the control group. Bioinformatic analysis showed that synthesis of lipids and steroids was activated in PCOS granulosa cells. Further analysis revealed that there was an approximate 25% reduction in global DNA methylation of granulosa cells in PCOS women compared with the controls. Hypomethylation of several gene promoters was shown related to lipid and steroid synthesis, which might result in the aberrant expression of these genes. It was finally suggested that hypomethylated genes related to the synthesis of lipid and steroid may dysregulate expression of these genes and promote synthesis of steroid hormones including androgen, which could partially explain mechanisms of hyperandrogenism in PCOS. In the deleterious reproductive consequences associated with exposure to environmental toxins such as BPA, changes in methylation of DNA may play a significant role. In neonatal rats, BPA exposure has been found to alter DNA methylation at key cell signaling genes, which increases the chance of developing precancerous prostatic lesions in adulthood. Neonatal exposure of BPA has been found to cause alterations to the epigenome in the frontal brain of mice. It has also been found that BPA alters reproduction-related gene expression and epigenetic modifications that are closely associated with infertility. BPA up-regulated mRNA expression of ESR1 gene. Another study showed that exposed human fetal oocytes to BPA showed up-regulated expression of ESR2 gene.

**CONCLUSION**

BPA is widely used in the daily household stuff and there is continuous exposure of these chemicals to the humans. The effect of exposure depends on the timing and duration of exposure. BPA acts through various mechanisms from receptor mediated to epigenetic alterations. Role of BPA in PCOS is increasingly convinced by multiple past and ongoing studies. Beyond doubt more number of studies are needed to validate the results of these studies. Till then the possible association of BPA induced changes through various mechanisms and pathways leading to PCOS cannot be ignored.

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**REFERENCES**


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