

PSYCHOLOGICAL VARIATIONS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Shriyanka Mishra, Himani Nautiyal* and Sanjay Singh

Department of Pharmacology, Siddhartha Nstitute of Pharmacy, Near T Park, Sahastradhara Road, Dehradun.

***Corresponding Author: Himani Nautiyal**

Department of Pharmacology, Siddhartha Nstitute of Pharmacy, Near T Park, Sahastradhara Road, Dehradun.

Article Received on 13/12/2021

Article Revised on 03/01/2022

Article Accepted on 24/01/2022

ABSTRACT

A higher percent range of reproductive age women (about 5.6-21.3%) are having Polycystic Ovary Syndrome. Dysfunction in ovaries and imbalances in hormones are resulted due to this PCOS condition. Hirsutism, menstrual irregularities, acne, infertility and alopecia are some magnified clinical symptoms due to PCOS. In this not only endocrine functions are altered but also psychological and reproductive systems also affected. Physical appearance and self-image of PCOS women gets affected by acne, hirsutism and obesity like conditions. Depression and sexual dissatisfaction like problems might also be developed due to PCOS. In the pathogenesis of PCOS compensatory hyperinsulinemia and insulin resistance play a significant role. This review article briefly discusses correlation of psychological alterations such as depression, anxiety, social fears and stress with PCOS. Various studies showed that adolescents are also mentally stressed at a more than normal level due to PCOS. Different psychopharmacological agents showed beneficial effects in psychic problems due to PCOS but not so much. Various case studies on psychological alterations showed higher prevalence of psychological disturbances. After studying and evaluating various journal articles and things from other sources it is suitable to say that problems are arising due to PCOS such as depression, anxiety etc. These problems can be recovered by screening or by further treatment measures. Approaching a psychiatrist may also be helpful for such people.

KEYWORDS: Polycystic Ovary Syndrome, Psychological, Stress, Depression, Alterations.**INTRODUCTION**

Affecting between 6.5 to 8 percent of women, PCOS is one of the most common disorders interrupting the homeostasis of the female endocrine system.^[1] This heterogeneous endocrinopathy begins at puberty and ends at menopause, with adverse sequel both in its clinical presentation and in its laboratory findings.^[2-6] Despite decades of research, there is no comprehensive explanation for the pathogenesis of this disorder. Most of the studies on PCOS focus on the endocrinopathy among affected women, and the underlying basis for the altered reproductive physiology is not sufficiently evaluated.

It is a heterogeneous clinical condition, with range of different phenotypes, a clinical reality that results in divergent opinions regarding diagnosis and treatment. Other potential features mentioned are: menstrual irregularity, subfertility, obesity, hirsutism, acne, and abnormal biochemistry, namely elevations of serum testosterone, androstenedione, luteinizing hormone, and insulin. The guidelines warn that affected women are at increased risk for hypertension, dyslipidemia, insulin resistance, glucose intolerance, type 2 diabetes, coagulation disorders, as well as cardiovascular morbidity and mortality.

Most studies on PCOS focus on the endocrinopathy among affected women, and the underlying basis for the altered reproductive physiology is not sufficiently evaluated.

Polycystic ovary syndrome (PCOS) is a complex genetic disease that affects approximately 7% of women of reproductive age worldwide.^[6] PCOS is a heterogeneous disorder, where the main clinical features include menstrual irregularities, subfertility, hyperandrogenism and hirsutism.^[7]

Polycystic ovary syndrome (PCOS), a disease that usually emerges during adolescence, is characterized by hormonal imbalance and ovarian dysfunction. The prevalence can vary between 5.6 to 21.3% in women and 6% in adolescent girls. This discrepancy is related to the population studied and the diagnostic criteria used.

The underlying pathophysiology of PCOS is not fully understood, but it can lead to a number of co-morbidities, including hypertension, diabetes, dyslipidemia, and also, mental health disorders. Clinical and preclinical data indicate neuroendocrine involvement with dysfunction in gamma-Aminobutyric acid (GABA) signaling and neuronal androgen receptors that might reduce

hypothalamic sensitivity and lead to an impairment of estradiol and progesterone feedback. There are several competing theories regarding the etiology of PCOS, but there is a consensus that the syndrome results from multiple causes. Significant interactions are likely among genetic and epigenetic factors, primary ovarian abnormalities, and neuroendocrine alterations.^[9] Recent evidence shows that neuroendocrine brain circuits, particularly the hypothalamic GnRH neuronal, are involved in the etiology of at least some forms of PCOS.^[10]

PCOS is a functional disorder in the growth and development of ovarian follicles leading to chronic anovulation.^[11] Insulin resistance (IR) and compensatory hyperinsulinemia play an important role in the pathogenesis of PCOS; hence, insulin-sensitising agents including metformin and thiazolidinediones are widely used in treating PCOS.^[12] In the past two decades, metformin has gained a great deal of interest from researchers because it has the capability to ameliorate IR and it has potential reproductive benefits in women with PCOS.

PCOS-related symptoms and complications can lead to mood disorders, eating disorders, social and marital conflicts, and sexual dysfunction,^[13-16] and they were confirmed to lead to significant reduction in quality of life (QoL).^[17-18]

Epidemiology

Globally- Data on the prevalence of PCOS are variable. This may be due, in part, to lack of well accepted criteria for diagnosis. The prevalence of PCOS varies between 2.5 & 11%. More recent European & American studies using NIH criteria are in agreement that PCOS is a common endocrine disorder, affecting women of reproductive age up to 6.8%.

In India- Indian study conducted by the department of endocrinology & metabolism, AIIMS, shows that about 20-25% of Indian women of childbearing age are suffering from PCOS.

While 60% of women with PCOS are obese, 35-50% have a fatty liver. About 70% have Insulin resistance, 60-70% have high level of androgen & 40-60 % have glucose intolerance.

Symptoms of Polycystic Ovary Syndrome^[20-30]

- Irregular periods or no periods at all
- Multiple Cysts
- Difficulty in getting pregnant
- Infertility
- Dark or thick skin patches on the back of neck, in the armpits, and under the breasts
- Mood change
- Anxiety
- Excessive hair growth (hirsutism)
- Weight gain

- Thinning hair and hair loss
- Oily skin or acne
- Fatigue
- Pelvic pain
- Headaches

Risk factors of Polycystic Ovary Syndrome^[25-35]

- Type-II diabetes
- Depression
- Endometrial carcinoma
- Poor body image impact on quality of life
- Sexual health challenges
- High blood pressure
- High cholesterol
- Heart disease
- Stroke
- Sleep apnoea
- Sedentary lifestyle
- Obesity

Complications

PCOS is the underlying cause in 75% of women with infertility owing to anovulation. Although women with PCOS may conceive, they are more at risk of pregnancy complications (e.g. preeclampsia, hypertension) than women without PCOS. Women with PCOS who are planning a pregnancy should be offered a 75g oral glucose tolerance test. This test should be repeated at 24–28 weeks gestation. Women with PCOS who experience fertility problems should be referred to a specialist. Owing to the abnormal hormone levels observed in PCOS, metabolic disease (i.e. glucose intolerance, type 2 diabetes mellitus or dyslipidaemia) and an increased cardiovascular risk are more common in women with the condition. Women with PCOS are also three times more likely to develop endometrial cancer compared with women without PCOS.

Some Existing Theories About Pathophysiology of Polycystic Ovary Syndrome

PCOS begins during the pubertal years, but the diagnosis is usually made later in life once the disorder has become relatively more severe. Ovarian dysfunction is thought to be caused by an impairment in the feedback loop of the steroid-hormone gonadotropin-releasing hormone (GnRH) produced in the hypothalamus. While there are other biologic systems and interconnected signaling networks also involved in the pathophysiology of PCOS, these latter networks may not be impaired in all affected women.^[41-43]

In healthy women, the frequency of GnRH pulses in the hypothalamus regulate the pulsatile release of Luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. Faster frequencies favor LH secretion and slower frequencies favor FSH release. In turn, LH and FSH secretion regulates the production of follicles and gonadal steroids in the ovary. The level of sex steroid hormones produced

by the ovaries-estrogens, progestogens, and androgens-provides critical feedback to the hypothalamus and pituitary gland, thus regulating the degree of GnRH, LH, and FSH secretion. In PCOS, this physiological feedback loop is compromised, resulting in hyperactivity of the hypothalamus-pituitary-gonadal axis and an abnormally high LH: FSH ratio. This then impairs follicle generation in the ovary and interferes with the production of steroid hormones.^[41]

The increased secretion of LH, acting on ovarian theca cells, stimulates the production of androgens. While androgens would normally be transformed into estradiol via an FSH-induced aromatase synthesized in ovarian granulosa cells, in women with PCOS, this transformation is impaired due to the altered LH/FSH ratio. This leads to a state of hyperandrogenism.^[44] It is unclear whether the problem starts with dysfunction in GnRH neurons in the hypothalamus or whether this occurs secondarily due to pathology of upstream neuronal systems.^[41]

What are Psychological Disorders?

The term psychological disorders is sometimes used to refer to what is more frequently known as mental disorders or psychiatric disorders. Mental disorders are patterns of behavioural or psychological symptoms that impact multiple areas of life. These disorders create distress for the person experiencing these disorders.

Neurodevelopmental Disorders

These are those that are typically diagnosed during infancy, childhood or adolescence. These psychological disorders include-

Intellectual Disability

Sometimes called Intellectual Developmental Disorder, this diagnosis was formerly referred to as mental retardation. This type of mental disorder originates prior to the age of 18 and is characterized by the limitations in both intellectual functioning and adaptive behaviors.

Limitations to intellectual functioning are often identified through the use of IQ tests, with an IQ score under 70 often indicating the presence of a limitation. Adaptive behaviors are those that involve practical, everyday skills such as self-care, social interaction, and living skills.

Bipolar Disorder

This disorder affects about 45 million people worldwide.^[85] It typically consists of both manic and depressive episodes separated by periods of normal mood. Manic episodes involve elevated or irritable mood, over-activity, rapid speech, inflated self-esteem and a decreased need for sleep. People who have manic attacks but do not experience depressive episodes are also classified as having bipolar disorder.

Effective treatments are available for the treatment of the acute phase of bipolar disorder and the prevention of

relapse. These are medicines that stabilize mood. Psychosocial support is an important component of treatment.

Schizophrenia and Other Psychosis

Schizophrenia is a severe mental disorder, affecting 20 million people worldwide¹. Psychoses, including schizophrenia, are characterized by distortions in thinking, perception, emotions, language, sense of self and behaviour. Common psychotic experiences include hallucinations (hearing, seeing or feeling things that are not there) and delusions (fixed false beliefs or suspicions that are firmly held even when there is evidence to the contrary). The disorder can make it difficult for people affected to work or study normally. Stigma and discrimination can result in a lack of access to health and social services. Furthermore, people with psychosis are at high risk of exposure to human rights violations, such as long-term confinement in institutions. Schizophrenia typically begins in late adolescence or early adulthood. Treatment with medicines and psychosocial support is effective. With appropriate treatment and social support, affected people can lead a productive life and be integrated in society. Facilitation of assisted living, supported housing and supported employment can act as a base from which people with severe mental disorders, including schizophrenia, can achieve numerous recovery goals as they often face difficulty in obtaining or retaining a place to live and normal employment.

Dementia

Worldwide, approximately 50 million people have dementia. Dementia is usually of a chronic or progressive nature in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.

Dementia is caused by a variety of diseases and injuries that affect the brain, such as Alzheimer's disease or stroke. Though there is no treatment currently available to cure dementia or to alter its progressive course, many treatments are in various stages of clinical trials. Much can be done, however, to support and improve the lives of people with dementia and their carers and families.

Risk Factors For Psychological Disorders^[5-10]

- Family or personal history of mental illness or substance abuse
- Intelligence below normal
- Low birth weight
- Lower socioeconomic status
- Parental absence, criminal activity, or substance abuse
- Prenatal exposures, such as to alcohol or drugs

- Significant medical conditions, such as cancer, chronic pain, and
- Hypothyroidism
- Social disadvantage
- Stressful or traumatic life events
- Substance abuse

Common Symptoms of Psychological Disorders^[1-10]

Psychological disorders can cause a variety of symptoms; common symptoms include-

- Agitation, hostility or aggression
- Alcohol or drug abuse
- Alterations in energy levels
- Anxiety
- Confusion or disconnectedness
- Erratic behavior
- Irritability and mood changes

Polycystic Ovary Syndrome With Psychological Burden

Psychosocial factors can play an important role in PCOS.

Numerous studies have evaluated the relation between PCOS and psychiatric disorders; however, most have evaluated psychiatric symptoms based on self-report measures.^[19-21]

PCOS is accompanied by an array of symptoms such as obesity, acne, scalp hair thinning, menstrual irregularity, and subfertility. These symptoms can also contribute to psychological impairment.^[22] Despite the use of antidepressants in the treatment of depressive symptoms, there has been only one report to date on the use of serotonin reuptake inhibitors with a successful outcome in a patient with PCOS.^[23] Relationship between PCOS and psychosocial problems has come to the attention of the medical community.^[24-25]

Neuroendocrine dysfunction has also been suggested, but the results are inconclusive.^[26-27] According to the literature, anxiety levels, psychological distress, including feelings of depression, and social fears are markedly higher in women with PCOS.^[28-33] Furthermore, several studies suggest that a proportion of the PCOS patients may present with clinically relevant psychopathology and impaired emotional well-being.^[34-35]

Sonino and colleagues showed that anxiety disorders in PCOS patients are common and that noticeable impairment of mental function may occur in these patients.^[36] These women are at an increased risk of psychological ill health which may markedly reduce their quality of life.^[37-38]

The contributing mechanisms for psychological disorders have not been completely understood, but they likely involve several pathways. Stress can be one of the mechanisms that induce psychological disorders via the

hypothalamic-pituitary-adrenal (HPA) axis and circadian pattern.

Psychiatric symptoms such as anxiety and depression are additional common features of the syndrome^[39-40], but they may be unrecognized by the treating physician. On the other hand, physicians who see patients for psychological problems may not ask about features of PCOS, or if they see clinical signs such as obesity, acne, and hirsutism, may automatically attribute them to the effects of psychiatric medications. Publications on comorbidity between PCOS and severe psychiatric disorders are more frequently seen in the gynecology and endocrinology literature than in papers on psychiatry. Lack of recognition of the co-existence of PCOS and psychiatric syndromes impacts negatively on affected women by delaying appropriate treatment. A large population-based study from Sweden found that 22.4% of the 22,385 women participants with PCOS had received at least one lifetime psychiatric diagnosis. When compared to a matched comparison sample, these women showed a higher prevalence not only of depression and anxiety, but also of less common disorders, such as bipolar disorder, schizophrenia spectrum disorder, eating disorder, and personality disorder.

There are several competing theories regarding the etiology of PCOS, but there is a consensus that the syndrome results from multiple causes. Significant interactions are likely among genetic and epigenetic factors, primary ovarian abnormalities, and neuroendocrine alterations.^[41] Recent evidence shows that neuroendocrine brain circuits, particularly the hypothalamic GnRH neuronal, are involved in the etiology of at least some forms of PCOS.^[42] Similar neuroendocrine dysfunctions of the hypothalamic-pituitary axis are found in psychotic disorder. Few studies, however, have assessed the impact on clinical, course and prognosis of comorbid PCOS and psychosis.

PCOS encompasses not only an endocrine condition, but also a reproductive and psychological syndrome for women with PCOS have their self-image and physical appearance changed by obesity, hirsutism and acne in addition to experiencing infertility. These symptoms occur with lifestyle changes that might generate sexual dissatisfaction and depression.^[45-46]

Many studies report an association between polycystic ovaries and high level of depression and anxiety, affecting quality of life and leading to a reduction of sleep and an increased incidence of phobias and panic.^[47] The relationship between affective disorders and the endocrine system has been extensively studied, and interest in this field has been growing in recent years. PCOS is a disorder closely related to women's physical appearances, causing a change in their body image that may lead to depression.^[48]

National literature about this subject is still scarce. A study conducted in Rio de Janeiro with 72 patients showed that 57% had at least one psychiatric diagnosis.^[49] Among the most frequent diagnoses were major depressive and bipolar disorders. Comorbidity of PCOS with a psychiatric disorder may increase functional damage. Similarly, some drug treatments for mood disorders have been reported to be associated with such syndrome's development.^[49]

Womens with Polycystic Ovary Syndrome and a Psychotic Disorder

Estrogen appears to exert an antipsychotic effect. When levels decline, the emergence of psychotic symptoms is facilitated.^[50] For instance, several literature reviews suggest that, in women with chronic psychotic illness, symptoms are aggravated during the premenstrual period^[51], after delivery^[51] and at menopause.^[50]

PCOS women, might, therefore, be vulnerable to psychosis because they are exposed to long durations of high levels of unopposed estrogen as a result of infrequent ovulation.^[52] When they do ovulate, they experience a precipitous reduction in estrogen, mimicking a postpartum state. This could explain the vulnerability of women with PCOS to psychotic symptoms.^[53]

Women with psychosis often show menstrual irregularity or amenorrhea, attributable to the hyperprolactinemia induced by the use of antipsychotic drugs.^[50] Hyperprolactinemia can also interfere with fertility^[54], a problem for up to 72% of PCOS women.^[55] Antipsychotic medications impact negatively on personal appearance because of associated weight gain, hirsutism, acne, dental problems, halitosis, alopecia, rash, tremor, stiff gait, unsightly mouth movements, voice changes, or incontinence.^[56-57] Similar symptoms are associated with PCOS, leading to a negative body image^[58], low self-esteem, perceived stigma^[59-60], and a high prevalence of anxiety and depression.^[61]

The high degree of symptom overlap between the two conditions may be what prevents the recognition of primary PCOS in psychiatric patients. Additionally, for women suffering from both conditions, these symptoms are all aggravated.

Mental Stress Among Adolescent With Polycystic Ovary Syndrome

PCOS-related mental stress is well studied by Himelein *et al.*,^[97] which indicates the symptoms of PCOS mostly affecting the patients include increased androgen levels, menstrual disturbances, infertility,^[98] obesity, hirsutism, or alopecia, but nowadays behavioral scientists start observing significant levels of mental stress in patients with PCOS,^[99] particularly among the young girls. This may be because young girls are more concerned about their physiology and physical health during adolescence. One of the studies reveals clear stress symptoms

explicated in a group of women who are having PCOS than the women who are not affected by PCOS.^[100] Depression and stress are the high-risk factors among the patients with PCOS along with the impaired metabolic and reproductive features. This high level of depression and anxiety in the patients with PCOS may be due to various reasons such as high BMI and demoralization faced by patients with PCOS in the society, which when severe may lead to social withdrawal. The clinical symptoms of PCOS, i.e., hyperandrogenism and infertility, add significantly to the severity of the conditions.^[101]

Management of Polycystic Ovary Syndrome Depression and Treatment in Adolescents

On the basis of recent management guidelines by Consensus on treatment of PCOS, the counseling related to the lifestyle changes, i.e., obesity control, daily walk, prevent smoking and alcohol consumption, clinical symptoms (menses irregularities) particularly in young girls, insulin resistance before medical treatment can produce positive outcomes^[102] by lowering the stress level in PCOS patients. Standard metformin treatment in PCOS cases if practiced regularly for 6 months can help to reduce various reproductive, physiological, and psychological problems.^[103] Several stress management interventions are also suggested to normalize Hypothalamic-Pituitary-Adrenal (HPA) axis at a normal pace, which may act as stressors by exaggerating Sympathetic Nervous System response in women with PCOS.^[104] It may include cognitive behavioral therapy and relaxation at the stage when standard metformin treatment fails to produce the expected stress relief in patients with PCOS.^[105]

The reason of distress along with the hirsutism among adolescents with PCOS is mostly due to the excess levels of androgens. Antiandrogen therapy can be carried out (if necessary) along with the cosmetic management^[106] (provided that hair removal method is authorized). The major challenge is the prevention of long-term complications of PCOS. The strong control of diet and an active lifestyle can effectively reduce the risk of diabetes in at-risk adults.^[107]

The Impact of Antipsychotic Medication Strategies

Besides increasing to PCOS-like symptoms, the chronic administration of antipsychotics has been shown to leave a negative impact on gut microbiota^[62-66], by enhancing the dysbiosis caused by PCOS. Though, Davey *et al.*^[64] clarified that the administration of olanzapine for 3 weeks in rats induced identifiable alterations in the microbiome. Antipsychotics have antibacterial properties. Olanzapine, for instance, is able to completely inhibit the growth of *E. coli*.^[66] For women with both conditions, hyperandrogenism could, in this way, be aggravated by the use of antipsychotics.

Infact, the weight gain induced by antipsychotics affects more than appearance. Elevated body mass index and

intra-abdominal adiposity predict insulin resistance and type 2 diabetes in the patients treated for long duration.^[67-68] Particular drugs (especially clozapine and olanzapine) are more likely than others to cause weight gain.^[69-70] Compared to untreated psychiatric controls, Galling and colleagues^[71] reported an incidence of T2DM three times higher in youth treated with antipsychotics for over three months.

Antipsychotic-induced diabetes has been confirmed in animal models, both olanzapine and clozapine have been shown to decrease the plasma level of insulin and to cause hyperglycemia and insulin resistance in rats.^[72]

Women with PCOS and without psychosis also show symptoms of obesity and insulin resistance, both conditions closely related to type 2 diabetes mellitus.^[73-74] The prevalence of overweight and obesity in PCOS is significantly greater than that of the general female population. Impaired glucose tolerance in women with PCOS was found to be 3-fold higher than in women of similar age by the National Health and Nutrition Survey II. When age and weight were controlled, the comparative prevalence was two-fold.^[74] Even lean women with PCOS show an increased risk for type 2 diabetes mellitus.^[75] The risk for women suffering from both PCOS and psychosis that requires antipsychotic treatment is very high.

Antipsychotic drugs predispose to metabolic syndrome^[71], to which women with PCOS are already susceptible.^[76] The available evidences found shows that dyslipidemia is very common in PCOS^[77], and that elevated values of triglycerides and total and low-density lipoprotein-cholesterol are frequently present. It is well known that dyslipidemia, obesity, and diabetes are all potent cardiovascular risk factors, but it is not currently certain whether the increased cardiovascular risk seen in PCOS is mediated through obesity or through other metabolic factors. Despite uncertainty about the pathway, the risk of cardiovascular illness is significantly elevated in PCOS^[78], as it is in patients with psychosis.

Cardiovascular disease is the major cause of mortality in patients with psychosis. The rate is approximately two times higher than it is in the general population^[79] and antipsychotic drugs are, at least in part, responsible.^[80-81] The similarities between both metabolic and cardiovascular side effects of patients in treatment for psychosis and patients with PCOS have profound health implications for women who suffer from both conditions.

Valproate can be used together or alone to treat bipolar disorder and it is known to induce PCOS-like symptoms. Therefore, patients maintained chronically on valproic acid should be monitored to avoid the development of menstrual irregularities and signs of PCOS, since the reproductive endocrine effects of valproate are reversible after the treatment is discontinued.^[82]

Although PCOS is the most frequent of all endocrine disorders among women of reproductive age, many women do not receive adequate treatment because of a too late diagnosis. To facilitate accurate diagnosis and timely treatment, clinicians who see female patients need to be familiar with the diversity of PCOS phenotypes. Patients with severe mental illness, on the other hand, have limited access to physical healthcare services.^[83] For this reason, it is important that psychiatrists be aware of the possibility of PCOS in their patients. When they learn about menstrual cycle irregularity in their women patients or find signs of hyperandrogenism, such as acne, hirsutism, and acanthosis nigricans^[84], they must not automatically attribute them to antipsychotic drug effects. Routine referral for a gynecology/endocrinology consult is indicated.

Moreover, for women with PCOS and psychosis, treatment with antipsychotic drugs can worsen PCOS symptomatology and lead to negative consequences for a woman's reproductive potential and her quality of life. Antipsychotic-induced weight gain is an important concern in the management of these patients.

Prevention of weight gain (choosing the right drug, keeping the dose as low as possible, instruction about diet, exercise, and substance use) is more effective than after-the-fact attempts at intervention. Adequate monitoring of body mass index, fasting glucose, and prolactin levels in patients on antipsychotics is vital for patients suffering from both conditions.

Various Case Studies on Psychological Alterations in Polycystic Ovary Syndrome

1st Case Study

Aditi P. Chaudhari et.al reported that a study done by Sundararaman et al. that^[86] had determined psychological distress in patients on the General Health Questionnaire and found it to be significantly related to obesity, infertility, acne, and hirsutism. On the other hand, a 2010 study by Bhattacharya and Jha^[87] assessed the impact of four symptoms, namely, obesity, acne, hirsutism, and acanthosis, only on depression, and found no significant association between the variables.

Seventy-five consecutive patients diagnosed with PCOS at the Department of Gynaecology were referred for evaluation. Seventy patients consented to be enrolled in the study. Thus, a total of 70 females in the age group of 18–45 years were studied. Of the 70 females studied, 27 were found to be suffering from anxiety disorders, while 18 were found to be suffering from depressive disorders. Thus, the prevalence of anxiety disorders in our study sample was 38.6%, and the prevalence of depressive disorders was 25.7%. Ten females (14.3%) suffered from both anxiety and depressive disorders. A total of 35 patients, that is, 50%, had neither of the two. The Hamilton rating scales for anxiety and depression were used to rate the severity of the respective conditions among those, in whom they were present. It was found

that mild, moderate, and severe anxiety was present in 62.90%, 29.60%, and 7.40%, respectively. On the other hand, 50% had mild, 38.8% had moderate, and 11.10% had severe depressive symptoms.

2nd Case Study

According to Saleha Sadeeqa et.al In adolescents, infrequent or absence of menstruation may raise chances for this condition. The increased prevalence of PCOS among general population throughout the world is found to be 5%–10% in the women of reproductive age, and about 40% women with PCOS experience depression, particularly young girls. Therefore, PCOS not only has problems associated with reproduction but also has associated crucial metabolic and psychological health risks with increasing age of the patients.

Studies revealed the increased prevalence of PCOS among the general population throughout the world, which ranges from 5% to 10%^[88] in women of reproductive age, and about 40% women with PCOS experience depression,^[89] particularly the young girls. The rate of PCOS in South-Western United States was found to be 4%. The incidence screened out to be 9.13% in Indian adolescents.^[90] As per the National Institute of Health, the rate of PCOS increases from 6.5% to 6.8% in adult reproductive-aged woman worldwide.^[91]

3rd Case Study

Atheena Mukundan et.al stated that Women with PCOS are more likely to have psychological disturbances, including depression generalized anxiety disorder and bring disorder, with a prevalence of 28%.^[92-94] Although, the exact association between PCOS and depression is unclear it is believed to be because of changes in physical features like hirsutism, alopecia, obesity, and acne, which influences the feminine identity and self-esteem.^[95-96]

A case-control study was carried out in 186 patients with PCOS, and 186 no BMI matched control group. The study was carried out in the Gynecology and Obstetrics Department of Employees State Insurance Corporation Hospital, Aynavaram, Chennai, Tamil Nadu from August 2017 to May 2018.

Around 372 women were enrolled in the study, including an equal number of women with PCOS (case) and women without PCOS (control), according to the inclusion and exclusion criteria. The study involved patients for whom the case reports were collected; depression was assessed and determinants. Also, the quality of life has been checked, where as in women without PCOS, the depression was the only parameter assessed along with basic demographic parameters.

In the study, about 76.96% of cases (women with PCOS) had depression compared to 20.03% of controls, odd's ratio 5.95 (95% confidence interval [3.818 to 9.351]). In them about 30.64% had minimal symptoms compared to

22.58%, 19.35% had minor depression compared to 3.225%, 16.12% had major depression compared to 1.61, and 4.83% had severe depression compared to 1.61% of control respectively.

In the study, most of the women shown depression were married (86.48%), and it was found to be having significantly associated with depression. Hirsutism was not found to be having an association with depression in PCOS and found anemia also doesn't have a significant association with depression. Having comorbidities like Diabetes Mellitus (80.01%) and Hypothyroidism (47.61%) found to be not significantly associated with depression. Most of the women with PCOS involved in the present study were found to be having infertility problems (93.33%), and it is having a significant association with developing depression in the study population.

In the study, depression was found to be less in the patients who were treating with OCP (56.66%) when compared with patients who are not treating with oral contraceptives (84.3%), and found to had an association with depression.

In the study, depression was found to be having an impact on patient's quality of life. About 3 of depressed patients had a mild decrease in quality of life compared to 36 of non-depressed patients, 51 of the depressed patients have a moderate decrease in quality of life and major decrease in quality of life compared to 15 and 3 of non-depressed patients respectively. 27 of the depressed patients had a severe decrease in quality of life whereas no non-depressed patients affected with severe decrease in quality of life.

DISCUSSION

According to the various studies it is now almost clear that women are facing various psychic problems with PCOS. Various evaluation of data showed that women who are of an healthy weight are also at higher risk for this problem.

In the studies, psychosocial kind of parameters were also studied in women without PCOS and with PCOS.

Data presented that PCOS is responsible with majority to cause severe type of depression and stress like problems.

Found evidences^[108-111] women who had PCOS, were at higher levels for psychological disorders.

Studies by Bhattacharya et.al^[111], higher depression ratio. Quality of life of such patients is also not very good. In the evaluation of their emotional state of health various difficulties comes such as their obesity, higher suicidal rate, poor self image in women with PCOS.^[112]

The pathophysiology of PCOS can provide a possible explanation for the observed increased risk of

psychological disturbances. Although the exact pathophysiological mechanism of PCOS is not fully understood,^[113] there are many theories that have been proposed to explain the pathogenesis of PCOS. One theory states that there is an alteration in gonadotropin releasing hormone secretion, which results in increased luteinizing hormone (LH) secretion, leading to the production of more androgens.^[115] Another theory states that a high insulin level also suppresses hepatic production of sex hormone binding globulin, leading to an increase in the unbound level of testosterone that subsequently results in hirsutism and acne.^[113] Empirically, evidence has suggested that both high insulin and androgen change monoamine balance, which is known to result in mood disturbances in PCOS patients.^[114]

CONCLUSION

Menstrual irregularities, androgen level imbalances and depression like symptoms are common features of PCOS. In the patients who have impaired reproductive and metabolic functions they are more susceptible to face stress problems. In adolescents emotional stress and depression was considered to be caused by obesity factor.

Patients who are more likely to suffer with such problems must be counseled by psychiatrist or any other caregiver to enhance feeling of well being in such patients till long time. Many factors such as infertility problems, marital status, age etc. were also responsible for causing psychological problems in patients with PCOS. So if things will be initiated to overcome these problems and correction in such factors they patients are at high chance to get good quality of life and release from depression.

If depression like symptoms will be identified soon in such patients then not only it will improve quality of life but also reduce cost for treatment.

REFERENCES

1. R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of clinical endocrinology and metabolism*, 2004; 89(6): 2745–9. doi: 10.1210/jc.2003-032046. [PubMed] [CrossRef] [Google Scholar]
2. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu Rev Nutr.*, 2005; 25: 391–406. doi: 10.1146/annurev.nutr.24.012003.132155. [PubMed] [CrossRef] [Google Scholar]
3. Franks S. Diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria. *The Journal of clinical endocrinology and metabolism*, 2006; 91(3): 786–9. doi: 10.1210/jc.2005-2501. [PubMed] [CrossRef] [Google Scholar]
4. Lee AT, Zane LT. Dermatologic manifestations of polycystic ovary syndrome. *Am J Clin Dermatol*, 2007; 8(4): 201–19. [PubMed] [Google Scholar]
5. Diamanti-Kandarakis E, Economou F. Stress in women: metabolic syndrome and polycystic ovary syndrome. *Annals of the New York Academy of Sciences*, 2006; 1083: 54–62. doi: 10.1196/annals.1367.006. [PubMed] [CrossRef] [Google Scholar]
6. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. *Obes Facts*, 2009; 2(1): 26–35. doi: 10.1159/000194971. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Dunaif A. Polycystic ovary syndrome in 2011: genes, aging and sleep apnea in polycystic ovary syndrome. *Nat Rev Endocrinol*, 2012; 8(2): 72–74. [PubMed] [Google Scholar]
8. Ali AT. Polycystic ovary syndrome and metabolic syndrome. *Ceska Gynekol*, 2015; 80(4): 279–289. [PubMed] [Google Scholar]
9. Coyle C, Campbell RE. Pathological pulses in PCOS. *Mol Cell Endocrinol*, 2019; 498: 110561. doi: 10.1016/j.mce.2019.110561
10. Nordholm D, Rostrup E, Mondelli V, Randers L, Nielsen M, Wulff S, et al. Multiple measures of HPA axis function in ultra high risk and first-episode schizophrenia patients. *Psychoneuroendocrinology*, 2018; 92: 72–80. doi: 10.1016/j.psyneuen.2018.03.015
11. Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2011.
12. Diamanti-Kandarakis E, Papavassiliou AG. Molecular mechanisms of insulin resistance in polycystic ovary syndrome. *Trends Mol Med.*, 2006; 12: 324–32.
13. Balikci A, Erdem M, Keskin U, et al. Depression, Anxiety, and Anger in Patients with Polycystic Ovary Syndrome. *Noro Psikiyatr Ars*, 2014; 51: 328–3.
14. Veltman-Verhulst SM, Boivin J, Eijkemans MJ, et al. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. *Hum Reprod Update*, 2012; 18: 638–51.
15. Drosdzol A, Skrzypulec V, Mazur B, et al. Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. *Folia Histochem Cytobiol*, 2007; 45(1): S93–7.
16. Lee I, Cooney LG, Saini S, et al. Increased risk of disordered eating in polycystic ovary syndrome. *Fertil Steril*, 2017; 107: 796–802.
17. Li Y, Li Y, Yu Ng EH, et al. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil Steril*, 2011; 96: 452–8.
18. Panico A, Messina G, Lupoli GA, et al. Quality of life in overweight (obese) and normal-weight

- women with polycystic ovary syndrome. *Patient Prefer Adherence*, 2017; 11: 423–9.
19. Dunaif A. Polycystic ovary syndrome in 2011: genes, aging and sleep apnea in polycystic ovary syndrome. *Nat Rev Endocrinol*, 2012; 8(2): 72–74. [PubMed] [Google Scholar]
 20. Ali AT. Polycystic ovary syndrome and metabolic syndrome. *Ceska Gynekol*, 2015; 80(4): 279–289. [PubMed] [Google Scholar]
 21. Annagur BB, Kerimoglu OS, Tazegul A, Gunduz S, Gencoglu BB. Psychiatric comorbidity in women with polycystic ovary syndrome. *J Obstet Gynaecol Res.*, 2015; 41(8): 1229–1233. [PubMed] [Google Scholar]
 22. Naqvi SH, Moore A, Bevilacqua K, et al. Predictors of depression in women with polycystic ovary syndrome. *Arch Womens Ment Health*, 2015; 18(1): 95–101. [PubMed] [Google Scholar]
 23. Blay SL. A case of major depressive disorder and symptoms of polycystic ovary syndrome responding to escitalopram. *Prim Care Companion CNS Disord*, 2011; 13(6). [PMC free article] [PubMed] [Google Scholar]
 24. Moreira S, Soares E, Tomaz G, Maranhão T, Azevedo G. [Polycystic ovary syndrome: a psychosocial approach] *Acta medic portuguesa*, 2010; 23(2): 237–42. [PubMed] [Google Scholar]
 25. de Niet JE, de Koning CM, Pastoor H, Duivenvoorden HJ, Valkenburg O, Ramakers MJ. et al. Psychological well-being and sexarche in women with polycystic ovary syndrome. *Humreprod*, 2010; 25(6): 1497–503. doi: 10.1093/humrep/deq068. [PubMed] [CrossRef] [Google Scholar]
 26. Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. *Psychosomatic medicine*, 2004; 66(3): 356–62. [PubMed] [Google Scholar]
 27. Mansson M, Holte J, Landin-Wilhelmsen K, Dahlgren E, Johansson A, Landen M. Women with polycystic ovary syndrome are often depressed or anxious--a case control study. *Psychoneuroendocrinology*, 2008; 33(8): 1132–8. doi: 10.1016/j.psyneuen.2008.06.003. [PubMed] [CrossRef] [Google Scholar]
 28. Jedel E, Waern M, Gustafson D, Landén M, Eriksson E, Holm G. et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. *Human reproduction (Oxford, England)*, 2010; 25(2): 450–6. doi: 10.1093/humrep/dep384. [PubMed] [CrossRef] [Google Scholar]
 29. Janssen OE, Hahn S, Tan S, Benson S, Elsenbruch S. Mood and sexual function in polycystic ovary syndrome. *Seminars in reproductive medicine*, 2008; 26(1): 45–52. doi: 10.1055/s-2007-992924. [PubMed] [CrossRef] [Google Scholar]
 30. Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. *Fertil Steril*, 2009; 91(1): 207–12. doi: 10.1016/j.fertnstert.2007.11.022. [PubMed] [CrossRef] [Google Scholar]
 31. 21. Himelein MJ, Thatcher SS. Polycystic ovary syndrome and mental health: A review. *Obstet Gynecol Surv*, 2006; 61(11): 723–32. doi: 10.1097/01.ogx.0000243772.33357.84. [PubMed] [CrossRef] [Google Scholar]
 32. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil Steril*, 2010; 93(7): 2421–3. doi: 10.1016/j.fertnstert.2009.09.018. [PubMed] [CrossRef] [Google Scholar]
 33. Rassi A, Veras AB, dos Reis M, Pastore DL, Bruno LM, Bruno RV. et al. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. *Compr Psychiatry*, 2010; 51(6): 599–602. doi: 10.1016/j.comppsy.2010.02.009. [PubMed] [CrossRef] [Google Scholar]
 34. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology*, 2005; 30(1): 1–10. doi: 10.1016/j.psyneuen.2004.05.007. [PubMed] [CrossRef] [Google Scholar]
 35. Diamanti-Kandarakis E. PCOS in adolescents. *Best Pract Res Clin Obstet Gynaecol*, 2010; 24(2): 173–83. doi:10.1016/j.bpobgyn.2009.09.005. [PubMed] [CrossRef] [Google Scholar]
 36. Sonino N, Navarrini C, Ruini C, Ottolini F, Paoletta A, Fallo F. et al. Persistent psychological distress in patients treated for endocrine disease. *Psychotherapy Psychosomatics*, 2004; 73(2): 78–83. doi: 10.1159/000075538. [PubMed] [CrossRef] [Google Scholar]
 37. Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. *Hum Reprod Update*, 2008; 14(1): 15–25. doi: 10.1093/humupd/dmm030. [PubMed] [CrossRef] [Google Scholar]
 38. Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS) *Fertil Steril*, 2010; 94(1): 357–9. doi: 10.1016/j.fertnstert.2009.09.025. [PubMed] [CrossRef] [Google Scholar]
 39. Cesta CE, Månsson M, Palm C, Lichtenstein P, Iliadou AN, Landén M. Polycystic ovary syndrome and psychiatric disorders: Comorbidity and heritability in a nationwide Swedish cohort. *Psychoneuroendocrinology*, 2016; 73: 196–203. doi: 10.1016/j.psyneuen.2016.08.005
 40. Blay SL, Aguiar JVA, Passos IC. Polycystic ovary syndrome and mental disorders: A systematic review and exploratory meta-analysis. *Neuropsychiatr Dis Treat*, 2016; 12: 2895–903. doi: 10.2147/NDT.S91700
 41. Coyle C, Campbell RE. Pathological pulses in PCOS. *Mol Cell Endocrinol*, 2019; 498: 110561. doi: 10.1016/j.mce.2019.110561

42. Nordholm D, Rostrup E, Mondelli V, Randers L, Nielsen M, Wulff S, et al. Multiple measures of HPA axis function in ultra high risk and first-episode schizophrenia patients. *Psychoneuroendocrinology*, 2018; 92: 72–80. doi: 10.1016/j.psyneuen.2018.03.015
43. Witchel SF, Oberfield SE, Peña AS. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. *J Endocr Soc*, 2019; 3(8): 1545–73. doi: 10.1210/je.2019-00078
44. Ruddenklau A, Campbell RE. *Neuroendocrine Impairments of Polycystic Ovary Syndrome*. *Endocrinology*: Oxford University Press, 2019; 160: 2230–42.
45. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil Steril*, 2010; 93(7): 2421–3.
46. Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *Eur J Endocrinol*, 2005; 153(6): 853–60.
47. Jedel E, Waern M, Gustafson D, Landén M, Eriksson E, Holm G, et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. *Hum Reprod*, 2010; 25(2): 450–6.
48. Rasgon NL, Rao RC, Hwang S, Altshuler LL, Elman S, Zuckerbrow-Miller J, et al. Depression in women with polycystic ovary syndrome: clinical and biochemical correlates. *J Affect Disord*, 2003; 74(3): 299–304.
49. Rassi A, Veras AB, dos Reis M, Pastore DL, Bruno LM, Bruno RV, et al. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. *Compr Psychiatry*, 2010; 51(6): 599–602.
50. Riecher-Rössler A. Oestrogens, prolactin, hypothalamic-pituitary-gonadal axis, and schizophrenic psychoses. *Lancet Psychiatry Elsevier Ltd.*, 2017; 4: 63–72. doi: 10.1016/S2215-0366(16)30379-0.
51. Seeman MV. Menstrual exacerbation of schizophrenia symptoms. *Acta Psychiatr Scand*, 2012; 125(5): 363–71. doi: 10.1111/j.1600-0447.2011.01822.x.
52. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update*, 2008; 14(4): 367–78. doi: 10.1093/humupd/dmn015.
53. Deuchar N, Brockington I. Puerperal and menstrual psychoses: The proposal of a unitary etiological hypothesis. *J Psychosom Obstet Gynaecol*, 1998; 19(2): 104–10. doi: 10.3109/01674829809048503
54. Zhang-Wong JH, Seeman MV. Antipsychotic drugs, menstrual regularity and osteoporosis risk. *Arch Womens Ment Health*, 2002; 5(3): 93–8. doi: 10.1007/s00737-002-0002-4
55. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: Data from a large community-based cohort study. *J Women's Heal*, 2015; 24(4): 299–307. doi: 10.1089/jwh.2014.5000
56. Haddad PM, Sharma SG. Adverse Effects of Atypical Antipsychotics Differential Risk and Clinical Implications. *CNS Drugs*, 2007; 21(11): 911–36. doi: 10.2165/00023210-200721110-00004
57. Seeman MV. Antipsychotics and physical attractiveness. *Clin Schizophr Relat Psychoses*, 2011; 5(3): 142–6. doi: 10.3371/CSRP.5.3.4
58. Moran L, Gibson-Helm M, Teede H, Deeks A. Polycystic ovary syndrome: A biopsychosocial understanding in young women to improve knowledge and treatment options. *J Psychosom Obstet Gynecol*, 2010; 31(1): 24–31. doi: 10.3109/01674820903477593
59. Conaglen HM, Conaglen JV. Sexual desire in women presenting for antiandrogen therapy. *J Sex Marital Ther.*, 2003; 29(4): 255–67. doi: 10.1080/00926230390195498
60. Chachamovich JR, Chachamovich E, Ezer H, Fleck MP, Knauth D, Passos EP. Investigating quality of life and health-related quality of life in infertility: A systematic review. *J Psychosom Obstet Gynecol*, 2010; 31(2): 101–10. doi: 10.3109/0167482X.2010.481337
61. Veltman-verhulst SM, Boivin J, Eijkemans MJC, Fauser BJCM. Emotional distress is a common risk in women with polycystic ovary syndrome: A systematic review and meta-analysis of 28 studies. *Hum Reprod Update*, 2012; 18(6): 638–51. doi: 10.1093/humupd/dms029
62. Bahr SM, Tyler BC, Wooldridge N, Butcher BD, Burns TL, Teesch LM, et al. Use of the second-generation antipsychotic, risperidone, and secondary weight gain are associated with an altered gut microbiota in children. *Transl Psychiatry*, 2015; 5(9): e652–6. doi: 10.1038/tp.2015.135
63. Davey KJ, Cotter PD, O'Sullivan O, Crispie F, Dinan TG, Cryan JF, et al. Antipsychotics and the gut microbiome: Olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. *Transl Psychiatry*, 2013; 3: 1–7. doi: 10.1038/tp.2013.83
64. Davey KJ, O'Mahony SM, Schellekens H, O'Sullivan O, Bienenstock J, Cotter PD, et al. Gender-dependent consequences of chronic olanzapine in the rat: Effects on body weight, inflammatory, metabolic and microbiota parameters. *Psychopharmacol (Berl)*, 2012; 221(1): 155–69. doi: 10.1007/s00213-011-2555-2
65. Kao ACC, Spitzer S, Anthony DC, Lennox B, Burnet PWJ. Prebiotic attenuation of olanzapine-induced weight gain in rats: Analysis of central and peripheral biomarkers and gut microbiota. *Transl Psychiatry*, 2018; 8(1). doi: 10.1038/s41398-018-0116-8
66. Morgan AP, Crowley JJ, Nonneman RJ, Quackenbush CR, Miller CN, Ryan AK, et al. The

- antipsychotic olanzapine interacts with the gut microbiome to cause weight gain in mouse. *PLoS One*, 2014; 9(12): 1–20. doi: 10.1371/journal.pone.0115225
67. Bou Khalil R. Atypical antipsychotic drugs, schizophrenia, and metabolic syndrome in non-euro-american societies. *Clin Neuropharmacol*, 2012; 35(3): 141–7. doi: 10.1097/WNF.0b013e31824d5288
 68. Manu P, Correll CU, van Winkel R, Wampers M, Hert M De. Prediabetes in Patients Treated With Antipsychotic Drugs. *J Clin Psychiatry*, 2012; 73(04): 460–6. doi: 10.4088/JCP.10m06822
 69. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *Lancet*, 2013; 382(9896): 951–62. doi: 10.1016/S0140-6736(13)60733-3
 70. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: A drug safety review. *Expert Opin Drug Saf.*, 2015; 14(1): 73–96. doi: 10.1517/14740338.2015.974549
 71. Gallig B, Roldán A, Nielsen RE, Nielsen J, Gerhard T, Carbon M, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: A systematic review and meta-analysis. *JAMA Psychiatry*, 2016; 73(3): 247–59. doi: 10.1001/jamapsychiatry.2015.2923
 72. Seeman MV. Menstrual exacerbation of schizophrenia symptoms. *Acta Psychiatr Scand*, 2012; 125(5): 363–71. doi: 10.1111/j.1600-0447.2011.01822.x
 73. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. *Lancet*, 2014; 383(9922): 1068–83. doi: 10.1016/S0140-6736(13)62154-6
 74. Verma S, Hussain ME. Obesity and diabetes: An update. *Diabetes Metab Syndr Clin Res Rev.*, 2017; 11(1): 73–9. doi: 10.1016/j.dsx.2016.06.017
 75. Zhang N, Shi YH, Hao CF, Gu HF, Li Y, Zhao YR, et al. Association of +45G15G(T/G) and +276(G/T) polymorphisms in the ADIPOQ gene with polycystic ovary syndrome among Han Chinese women. *Eur J Endocrinol*, 2008; 158(2): 255–60. doi: 10.1530/EJE-07-0576
 76. Bhattacharya SM. Metabolic syndrome in females with polycystic ovary syndrome and International Diabetes Federation criteria. *J Obstet Gynaecol. Res.*, 2008; 34(1): 62–6. doi: 10.1111/j.1447-0756.2007.00685.x
 77. Dunaif A, Legro RS. Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome—Authors' Response. *J Clin Endocrinol Metab*, 1999; 84(8): 297–2976. doi: 10.1210/jc.84.8.2975
 78. Orio F, Palomba S, Colao A. Cardiovascular risk in women with polycystic ovary syndrome. *Fertil. Steril*, 2006; 86: S20–1. doi: 10.1016/j.fertnstert.2006.03.003
 79. Page H, Morgan C, Lappin J, Dazzan P, Murray R, Fearon P. @ a Systematic Review of Coping in Schizophrenia. *Schizophr Res.*, 2008; 102(1–3): 218. doi: 10.1016/S0920-9964(08)70659-5
 80. Johannesen L, Garnett C, Luo M, Targum S, Sørensen JS, Mehrotra N. Quantitative Understanding of QTc Prolongation and Gender as Risk Factors for Torsade de Pointes. *Clin Pharmacol Ther.*, 2018; 103(2): 304–9. doi: 10.1002/cpt.783
 81. Axelsson S, Hägg S, Eriksson AC, Lindahl TL, Whiss PA. In vitro effects of antipsychotics on human platelet adhesion and aggregation and plasma coagulation. *Clin Exp Pharmacol Physiol*, 2007; 34(8): 775–80. doi: 10.1111/j.1440-1681.2007.04650.x
 82. Joffe H, Hayes FJ. Menstrual Cycle Dysfunction Associated with Neurologic and Psychiatric Disorders. *Ann IN Y Acad Sci.*, 2008; 1135(1): 219–29. doi: 10.1196/annals.1429.030
 83. De Hert M, Cohen D, Bobes J, Cetrovik-Barmas M, Leucht S, Ndeti DM, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry*, 2011; 10(2): 138–51. doi: 10.1002/j.2051-5545.2011.tb00036.x
 84. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, et al. Polycystic ovary syndrome. *Nat Rev Dis Prim.*, 2016; 2. doi: 10.1038/nrdp.2016.57
 85. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study, 2017.
 86. Sundararaman PG, Shweta, Sridhar GR. Psychosocial aspects of women with polycystic ovary syndrome from South India. *J Assoc Physicians India*, 2008; 56: 945–8. [PubMed] [Google Scholar]
 87. Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS) *Fertil Steril*, 2010; 94: 357–9. [PubMed] [Google Scholar]
 88. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*, 2004; 89: 2745–9. [PubMed] [Google Scholar]
 89. Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. *Fertil Steril*, 2009; 91: 207–12. [PubMed] [Google Scholar]
 90. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. *J Pediatr Adolesc Gynecol*, 2011; 24: 223–7. [PubMed] [Google Scholar]

91. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab*, 2000; 85: 2434–8. [PubMed] [Google Scholar]
92. Lee I, Cooney LG, Saini S, Smith ME, Sammel MD, Allison KC and Dokras A: Increased risk of disordered eating in polycystic ovary syndrome, 2017; 107(3): 796-02.
93. Cooney LG, Lee I, Sammel MD and Dokras A: High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis, *Human Reproduction*, 2017; 5(1): 1075-91.
94. Bhat A, Reed SD and Unützer J: The Obstetrician–Gynecologist’s role in detecting, preventing, and treating depression. *Obstetrics & Gynecology*, 2017; 129(1): 157-63.
95. Blay SL, Aguiar JVA and Passos IC: Polycystic ovary syndrome and mental disorders: a systematic review and exploratory meta-analysis. *Neuropsychiatric Disease and Treatment*, 2016; 12: 2895.
96. Jalilian A, Kiani F, Fatemeh Sayehmiri F, Sayehmiri K, Zahra Khodae Z and Akbari M: Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis *Iran J Reprod Med.*, 2015; 13(10): 591-04.
97. Himelein MJ, Thatcher SS. Polycystic ovary syndrome and mental health: a review. *Obstet Gynecol Surv*, 2006; 61: 723–32. [PubMed] [Google Scholar]
98. Trent ME, Austin B, Rich M, Gordon CM. Overweight status of adolescent girls with polycystic ovary syndrome: body mass index as mediator of quality of life. *Ambu Pediat*, 2005; 5: 107–11. [PubMed] [Google Scholar]
99. Franks S. Polycystic ovary syndrome in adolescents. *Int J Obes (Lond)*, 2008; 32: 1035–41. [PubMed] [Google Scholar]
100. Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. *Psychosom Med.*, 2004; 66: 356–62. [PubMed] [Google Scholar]
101. Jones G, Balen A, Ledger W. Health-related quality of life in PCOS and related infertility: how can we assess this? *Human Fertil*, 2008; 15: 173–85. [PubMed] [Google Scholar]
102. Motta B. Metformin in the treatment of polycystic ovary syndrome. *Cur Pharm Des.*, 2008; 14: 2121–5. [PubMed] [Google Scholar]
103. Hahn S, Benson S, Elsenbruch S, Pleger K, Tan S, Mann K, et al. Metformin treatment of polycystic ovary syndrome improves health-related quality-of-life, emotional distress and sexuality. *Hum Reprod*, 2006; 21: 1925–34. [PubMed] [Google Scholar]
104. Phillips KM, Antoni MH, Lechner SC, Blomberg BB, Llabre MM, Avisar E, et al. Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. *Psychosom Med.*, 2008; 70: 1044–9. [PMC free article] [PubMed] [Google Scholar]
105. Benson S, Arck PC, Tan S, Hahn S, Mann K, Rifaie N, et al. Disturbed stress responses in women with polycystic ovary syndrome. *Psychoneuroendocrinology*, 2009; 34: 727–35. [PubMed] [Google Scholar]
106. Koulouri O, Conway GS. A systematic review of commonly used medical treatments for hirsutism in women. *Clin Endocrinol (Oxf)*, 2008; 68: 800–5. [PubMed] [Google Scholar]
107. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *Scand Med Sci in Spor*, 2003; 13: 208. [PMC free article] [PubMed] [Google Scholar]
108. Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. *Fertil Steril*, 2009; 91(1): 207–12. doi: 10.1016/j.fertnstert.2007.11.022. [PubMed] [CrossRef] [Google Scholar]
109. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil Steril*, 2010; 93(7): 2421–3. doi: 10.1016/j.fertnstert.2009.09.018. [PubMed] [CrossRef] [Google Scholar]
110. Rassi A, Veras AB, dos Reis M, Pastore DL, Bruno LM, Bruno RV. et al. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. *Compr Psychiatry*, 2010; 51(6): 599–602. doi: 10.1016/j.comppsy.2010.02.009. [PubMed] [CrossRef] [Google Scholar]
111. Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS) *Fertil Steril*, 2010; 94(1): 357–9. doi: 10.1016/j.fertnstert.2009.09.025. [PubMed] [CrossRef] [Google Scholar]
112. Bazarganipour F, Ziaei S, Montazeri A, Foroozanfard F, Kazemnejad A, Faghihzadeh S. Body image satisfaction and self-esteem status among the patients with polycystic ovary syndrome. *Iran J Reprod Med.*, 2013; 11(10): 829–836. [PMC free article] [PubMed] [Google Scholar]
113. Balen A. The pathophysiology of polycystic ovary syndrome: trying to understand PCOS and its endocrinology. *Best Pract Res Clin Obstet Gynaecol*, 2004; 18(5): 685–706.
114. Kocelak P, Chudek J, Naworska B, et al. Psychological disturbance and quality of life in obese and infertile women and men. *Int J Endocrinol*, 2012; 2014: 14.
115. Ehrmann DA. Polycystic ovary syndrome. *n Engl J Med.*, 2005; 352(12): 1223–1236.