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Psychiatric disorders in women with polycystic ovary syndrome

Daniel Rodriguez-Paris[1], Agnieszka Remlinger-Molenda[2], Rafał Kurzawa[3], Aleksandra Głowińska[4], Robert Spaczyński[5], Filip Rybakowski[2], Leszek Pawelczyk[5], Beata Banaszewska[5]

[1] Provincial Neuropsychiatric Hospital in Koscian
[2] Poznan University of Medical Sciences, Department of Adult Psychiatry
[3] Pomeranian Medical University in Szczecin, Department of Gynecology and Reproductive Health
[4] Gynecological and Obstetrical Clinical Hospital in Poznan, Department of Psychology
[5] Poznan University of Medical Sciences, Department of Infertility and Reproductive Endocrinology

Summary

Polycystic ovary syndrome (PCOS) is the most commonly diagnosed endocrine disorder in women of reproductive age, affecting approximately 5–8% of females in this group. It is characterized by hyperandrogenism, abnormal periods (rare periods or amenorrhea) and polycystic ovaries visualized through ultrasonography. The etiopathogenesis of polycystic ovary syndrome has not been elucidated in detail. There are numerous hypotheses on this subject which tend to complement one another. The most widely recognized hypothesis is that the development of PCOS is due to insulin resistance and hyperinsulinemia, which subsequently lead to hyperandrogenism. On the basis of an as of yet relatively small number of studies, an increased prevalence of various psychiatric disorders can be observed in women with PCOS. These include: depression, generalized anxiety disorder, personality disorders, social phobia, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), and eating disorders. Bipolar affective disorder, schizophrenia and other psychotic disorders have also been reported in women with PCOS more often than in the general population. The higher prevalence of psychiatric disorders in patients with PCOS, especially depression and anxiety disorders, may be due to both hyperandrogenism and the resulting somatic symptoms. These symptoms can undoubtedly be stigmatizing for women and lower their quality of life. This article is intended to provide an overview of the literature regarding mental disorders associated with polycystic ovary syndrome and to present own research on depression and sexual dysfunction in this group.

Key words: PCOS, mood disorders, other psychiatric disorders

Introduction

Polycystic ovary syndrome (PCOS) is the most commonly diagnosed endocrine disorder in women of reproductive age, affecting approximately 5–8% of females [1]. It is characterized by hyperandrogenism, chronic anovulation (rare periods or amenorrhea) and polycystic ovaries visualized through ultrasonography. Diagnosis of PCOS is currently based on the Rotterdam criteria, established in 2003, and its utilization has resulted in the recognition of several distinct clinical phenotypes of this syndrome [2]. Previously, the diagnosis required the presence of both hyperandrogenism and menstrual disorders. Currently, according to the new definition, the diagnosis of polycystic ovary syndrome can be made by fulfilling two out of three criteria, the third being ultrasonographic evidence of polycystic ovaries. In this way, also a controversial phenotype of PCOS may be recognized, in which patients display chronic anovulation and polycystic ovaries but not hyperandrogenism. Broadening of the definition to include this phenotype has resulted in an overall increase in the estimated incidence of PCOS to 10% or more in the general population [3].

The etiopathogenesis of polycystic ovary syndrome has not been elucidated in detail. There are numerous hypotheses on this subject which tend to complement one another. The most widely recognized hypothesis is that the development of PCOS is due to insulin resistance and hyperinsulinemia which subsequently lead to hyperandrogenism. Currently, the most widely discussed theory involves prenatal exposure to elevated androgen levels [4]. The role of epigenetic factors in PCOS development during adolescence and adulthood is also emphasized. A third possibility is a genetic disorder, probably gene polymorphisms, which leads to the development of PCOS. An interesting observation is the presence of certain features of PCOS in the sisters of PCOS patients which meet PCOS diagnostic criteria in about 22–32% of cases [5, 6]. There is also evidence suggesting that a male counterpart of polycystic ovary syndrome exists. For example, brothers and fathers of PCOS patients are more likely to suffer from androgenic alopecia and display an unfavorable metabolic profile [7].

On the basis of an as of yet relatively small number of studies, an increased prevalence of various psychiatric disorders can be observed in women with PCOS. These include: depression, generalized anxiety disorder, personality disorders, social phobia, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), and eating disorders. Bipolar affective disorder, schizophrenia and other psychotic disorders have also been reported in women with PCOS more often than in the general population [8]. This article is intended to provide an overview of the literature regarding mental disorders in women with polycystic ovary syndrome.

Depression

The first pilot study on the occurrence of depression in women with PCOS was conducted by Natalie L. Rasgon of Stanford University on a group of 32 women with

clinically diagnosed polycystic ovary syndrome [9]. Depression was diagnosed on the basis of the Center for Epidemiological Studies-Depression Rating Scale (CES-D) in 16 of the 32 women. A co-dependence with insulin resistance and body mass index (BMI) was also demonstrated. Interestingly, the prevalence of depression was lower among women utilizing oral contraceptives. However, the most widely recognized work regarding depression in PCOS, published in 2007, was conducted by an American gynecologist Anuja Dokras et al. In this study, depression was diagnosed on the basis of the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [10]. 103 women with clinically diagnosed PCOS were assessed as well as a control group. Depression was observed in 21% of PCOS patients as compared to only 3% of healthy women. In 2011, the first meta-analysis on this subject was performed, examining 17 studies, involving a total of 522 PCOS patients and 475 controls [11]. The finding of this meta-analysis was that depression was four-times more common among women with polycystic ovarian syndrome.

In 2015, the Department of Infertility and Reproductive Endocrinology at the Poznan University of Medical Sciences published its first paper on depression in women with PCOS [12]. In this study, PCOS patients (n = 84) completed the Beck Depression Inventory (BDI) questionnaire. Symptoms of depression were noted in 52% of subjects. 32 women displayed mild symptoms, 8 moderate, and 2 severe symptoms. In 2015, Greenwood et al. [13] published a cross-sectional study assessing 301 women with PCOS which showed that 44% of women were at risk for depression based on the completion of the Beck Depression Inventory Fast Screen (BDI-FS). A significant correlation was noted between depression, insulin resistance (HOMA-IR) and BMI [13]. In 2015, Hart and Doherty [14] conducted a population-based retrospective cohort study, where they examined a large sample of 2,566 polycystic ovary syndrome patients hospitalized between1997 and 2011, and 25,660 randomly selected, age-matched women without a PCOS diagnosis. The study showed higher rates of various illnesses among PCOS patients such as: diabetes (12.5% vs. 3.8%), obesity (16.0% vs. 3.7%), hypertension (0.8% vs. 0.2%), asthma (10.6% vs. 4.5%), and depression (9.8% vs. 4.3%). The largest comprehensive study aimed at examining psychiatric comorbidity with PCOS, utilizing the Swedish national registers, was performed by Cesta et al. [8]. 24,385 PCOS subjects and 243,850 controls were assessed. The study showed that women with PCOS were at significantly increased risk for depression, including severe depression. The latest meta-analysis of 11 studies, published in 2017, was performed on a large representative sample of PCOS patients (3,050 subjects and 3,858 controls) from 10 different countries and confirmed previous findings [15]. The meta-analysis showed that the symptoms of depression, regardless of severity, were nearly four-times more common (the odds ratio (OR) was 3.78) among women with PCOS. An analysis of 18 studies regarding comorbidity of moderate and/or severe depression showed four-times higher risk of depression in women with PCOS (OR of 4.18) [15].

Anxiety disorders

One of the most commonly utilized diagnostic tools for assessing anxiety disorders is the State-Trait Anxiety Inventory (STAI) questionnaire, which allows for differentiation of state anxiety (STAI-S) versus trait anxiety (STAI-T). In 2011, a study on 130 women with PCOS was performed, which evaluated their hormonal and metabolic profiles as well as anxiety levels based on the STAI-T and the STAI-S [16]. Subjects with the highest STAI-S scores, compared to subjects with the lowest STAI-S scores, showed significantly higher levels of insulin resistance, based on the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) as well as the Free Androgen Index (FAI). Women with high STAI-T values also displayed significantly higher levels of insulin resistance. In 2012, Dokras et al. [17] published a meta-analysis on the association of PCOS with anxiety [17]. The prevalence of generalized anxiety disorder was assessed in four studies meeting the required criteria and was found to be significantly higher in patients with PCOS (42 out of 206, 20.4%) as compared to controls (8 out of 204, 3.9%).

In the 2016 publication by Głowińska et al. [12], which focused on determinants of emotional problems and mood disorders in women with PCOS, the average STAI score was 42.88 with a standard deviation of 10.35 (the measured scores were between 21 and 69), which corresponds to the STEN score of 7 (standard ten), which in turn corresponds to the mean anxiety levels for the Polish population [12]. An Australian study from 2015 showed a higher prevalence of anxiety disorders (14.0 vs. 5.9%) in a large group of patients with PCOS as compared to a control group [14]. The above-mentioned analysis by Cesta et al. [8] also confirmed a higher prevalence of anxiety disorders, including generalized anxiety disorders, which were by 58% more common in women with PCOS [8]. In the case of social phobias, the likelihood of their occurrence in PCOS patients was 43% higher. Rates of obsessive-compulsive disorder were also found to be 37% higher. The most recent meta-analysis by Dokras et al., published in 2017 [15], confirmed an almost six-times higher prevalence of anxiety disorders, regardless of their severity, in women with PCOS (OR = 5.62) [15]. In nine of the studies examined in the above-mentioned meta-analysis, the prevalence of moderate to severe anxiety disorders was found to be nearly seven-times higher in PCOS subjects (OR = 6.55).

Sexual dysfunction

Far fewer studies have been published on the topic of sexual dysfunction, as compared to those regarding depression or anxiety disorders. It can be inferred that certain phenotypical characteristics of women with PCOS, such as hirsutism, acne and/or obesity, can influence their emotional states and therefore indirectly affect the sexual function of these patients. In 2003, Elsenbruch et al. published the results of a study conducted on 50 women with PCOS and 50 controls [18]. He concluded that

the polycystic ovary syndrome was associated with severe limitations in sexual satisfaction. In 2010, a study by de Niet et al. [19] on a large sample of 480 women with PCOS was published. The study found that amenorrhea showed a strong correlation with low self-esteem, higher fear of social scrutiny, and earlier sexual initiation (sexarche). In 2012, Stovall published his work on the sexuality of women with PCOS [20]. The study involved 92 women with PCOS and 82 in the control group. The diagnostic tool used was the Changes in Sexual Functioning Questionnaire (CSF-Q), which included 14 questions assessing various aspects of sexual function: pleasure/satisfaction, desire/frequency, yearning/interest, arousal and orgasm/climax. Higher scores were associated with better sexual functionality. Based on data from this study, it can be concluded that there are not many differences in the sexual functioning of women with PCOS as compared to healthy women, with the exception of orgasm/climax. Conclusions from the study indicate that serum testosterone levels may play a significant role in sexual activity of women with PCOS. Further research is needed to determine the potential effects of BMI, acne and hirsutism on sexual function in this population.

In 2015, a meta-analysis on the subject of sexuality in women with PCOS was published, based albeit on limited comparative data, but suggesting that women with PCOS had a degree of impairment in terms of sexual arousal as compared to the control group [21]. No evidence of any other sexual dysfunctions was found. In a population study by Cesta et al. [8], it was found that women with PCOS had on average twice as many gender identity disorders as those without PCOS (OR = 2.02). An extremely interesting study was the work of Agrawal et al. published in 2004, which examined a sample of 618 women (254 homosexual and 364 heterosexual) referred for infertility treatment using intrauterine insemination [22]. Ultrasonographic imaging revealed that 80% of homosexual women displayed polycystic ovaries as compared to 32% of heterosexual women. In this study PCOS was diagnosed in 38% of homosexual women and only in 14% of heterosexual women. Higher androgen levels were also noted in homosexual women with polycystic ovary syndrome. On the other hand, data from the Epidemiologic Study of Health Risk (ESTHER) project, which analyzed a sample of 114 homosexual women and 97 heterosexual women, did not confirm a higher prevalence of PCOS in homosexual women [23].

Attention deficit hyperactivity disorder (ADHD)

Currently, there are very few publications on the prevalence of attention deficit hyperactivity disorder in women with polycystic ovary syndrome. One study assessed 40 women with PCOS and 40 healthy controls and found significantly higher scores on the adult ADHD scale in women with PCOS [24]. It was also determined, on the basis of the Wender–Utah Rating Scale, that the incidence of ADHD in childhood was greater in the PCOS group than in the control group.

Autism

The theory correlating increased androgen levels with autism suggests that women with PCOS may have a higher predisposition to this condition. Ingudomnukul et al. [25] examined 54 women with autism, 74 mothers of autistic children and 183 mothers of properly developing children. Higher rates of hirsutism, acne, menstrual disorders and elevated testosterone levels were found in autistic women and mothers of autistic children. In 2016, data from a Swedish population-based study were published, where 23,748 people with autism and 208,796 healthy controls were examined [26]. It was concluded that the children of mothers with PCOS had an increased risk of developing autism, regardless of gender. The above-mentioned population-based study by Cesta et al. [8] reported a more than two-times higher (OR = 2.09) prevalence of autism spectrum disorders, including a 57% (OR = 1.57) higher rate of the classic form of autism and an 80% (OR = 1.8) higher rate of Asperger's syndrome.

Eating disorders

In women with polycystic ovary syndrome, a higher prevalence of eating disorders has been observed. In a Swedish study assessing 11,503 women, it was determined that the prevalence of eating disorders is significantly correlated with amenorrhea ($p < 0.001$) and oligomenorrhea ($p < 0.001$) [27]. Cesta et al. [8] demonstrated a 35% greater prevalence of bulimia in women with PCOS (OR = 1.35). In 2017, a study was published that assessed a sample of 148 women with PCOS and 106 controls utilizing the Eating Disorder Examination Questionnaire (EDE-Q) [28]. It was shown that patients with PCOS, especially those with accompanying anxiety, but irrespective of body mass, have a significantly increased risk of abnormal EDE-Q scores.

Bipolar disorder

There are relatively few studies regarding bipolar affective disorder and PCOS, and their results are ambiguous. One of the reasons interest arose on this topic were more than a decade data suggesting a higher prevalence of polycystic ovary syndrome (PCOS) associated with valproate (VPA) use in both women with epilepsy and women with bipolar disorder [29]. However, much of the data were contrasting and no clear correlation was found. One of the first publications regarding PCOS and bipolar disorder was a pilot study by Klipstein and Goldberg in 2006 [30]. The study screened 78 women with diagnosed PCOS utilizing the Mood Disorders Questionnaire (MDQ) and found that 28% had either a prior diagnosis of bipolar disorder or met the diagnostic criteria.

In Iran, a case-control study was conducted on 110 women with PCOS and an identical number of age-matched infertile women [31]. Bipolar disorder was diagnosed in 8% of the PCOS group while none were found in the control group. Interestingly, in this study, the prevalence of depression was found to be higher in the control group. On the other hand, the cohort study published by Hung et al. in 2014

(5,431 PCOS patients and 21,724 controls), did not confirm a higher prevalence of bipolar affective disorder in the PCOS group [32]. The largest population survey of all psychiatric illnesses in PCOS women was conducted by Cesta et al. [8]. The study revealed an average of 91% higher prevalence of bipolar affective disorder in women with PCOS (OR = 1.91).

Schizophrenia

The first association of psychotic disorders with increased levels of testosterone and luteinizing hormone was observed in 1993 [33]. In 2011, the similarities between the pathogenesis of schizophrenia and the polycystic ovary syndrome were investigated [34]. 96 studies on schizophrenia and PCOS were taken into account. It was determined that insulin resistance and elevated testosterone levels were predictive factors for comorbidity of both disorders. The Swedish study also showed an 82% higher incidence of schizophrenia in women with PCOS (OR = 1.82) [8].

Other disorders

In regards to other psychiatric disorders, a study by Hart and Doherty [14], published in 2015, found higher rates of illicit drug-related admissions (8.8% vs. 4.5%) and self-harming behaviors (7.2% vs. 2.9%) in women with PCOS as compared to a much larger randomly selected age-matched population sample.

Recapitulation

The explanation for the increased risk of mental disorders among patients with PCOS remains difficult to interpret unambiguously. It is also known that there is an increased risk of the development of these disorders among siblings of PCOS patients. The source of the problem appears to be the adverse effects of androgens on brain development in the prenatal period. A possibility exists that elevated androgen levels cause changes in the brain's circuitry, leading to abnormal reactions to steroid hormones [35]. At critical stages, increased exposure to androgens in developing females may cause masculinization of the brain and, subsequently, behavior. Such a process has been demonstrated in animals [36, 37]. Androgen receptors are present in the perinatal and early postnatal female brain [38, 39]. Perhaps early exposure to androgens can permanently reorganize the female brain model and lead to overactivity of gonadoliberin (GnRH) neurons in adult life [35].

The higher prevalence of psychiatric disorders in patients with PCOS, especially depression and anxiety disorders, may be due to both hyperandrogenism and resulting somatic symptoms such as hirsutism, acne, male pattern baldness, deep voice or low stature (resulting from accelerated fusion of growth plates in long bones). These symptoms can undoubtedly be stigmatizing for women and lower their

quality of life. An interesting caveat is the fact that postmenopausal administration of androgens has been shown to have a positive effect on the sexual functionality [40]. Androgen deficient patients, after surgically induced menopause, experienced improved mental wellbeing, including increased psychomotor propulsion and elevation of mood after androgen supplementation. Patients with adrenal insufficiency treated with dehydroepiandrosterone also experienced an overall improvement in mood and increased libido [41]. The role of insulin resistance and obesity in the comorbidity of psychiatric disorders in women with PCOS is also being discussed. Chronic inflammatory states, which are often associated with obesity, may increase the concentration of proinflammatory cytokines and thereby exacerbate symptoms of depression and anxiety [42].

Poor mental health has significant socio-economic ramifications which affect individuals as well as society at large. The Global Burden of Disease Study 2010 (GBD 2010) estimated that mental, neurological and substance use disorders accounted for 10.4% of global disability-adjusted life years (DALYs), which is computed as the sum of years lived with disability (YLDs) and years lost to premature mortality (YLLs) [43]. Mental disorders comprised 57.6% of DALYs, and females accounted for more DALYs in all mental disorders, except for mental disorders occurring in childhood and schizophrenia. Mental disorder symptoms have been associated with a number of socio-economic factors such as employment status, economic hardship, poor social support, functional disability and overall reduced quality of life [44]. Traditionally, major health policy decisions have been primarily based on mortality statistics. Comparatively, little emphasis was made on morbidity, especially in the case of prevalent disorders with lower mortality rates such as mental and substance abuse disorders. As progress is made and new data become available, the need for implementation of early screening programs and establishment of cost-effective interventions is becoming apparent.

The association between polycystic ovary syndrome and various comorbidities including: infertility, obesity, type 2 diabetes, cardio-vascular disease, cancer, and psychological disorders, has been well established in scientific literature [45]. In October 2010, the third PCOS consensus workshop was held in Amsterdam with the goal of summarizing current knowledge and identifying gaps in knowledge regarding various health aspects of women with PCOS. One of the discussed topics focused on quality of life (QoL) of PCOS patients. One of the points of contention was whether the increased prevalence of psychological disorders was due to the syndrome itself or its manifestations (obesity, hirsutism, infertility, etc.). A recent study, published in 2018 by Greenwood et al., found a strong and independent association between insulin resistance and depression in PCOS [46]. However, the available data still do not elucidate the causality of such comorbidities. Attempts have been made at establishing more comprehensive mental health care programs for women with polycystic ovary syndrome. A three-phase study by ZareMobini et al. [47], utilizing a multidisciplinary team to analyze results, concluded that designing a program focused on improving

mental health and quality of life could be an important and cost-effective method of advanced treatment of PCOS patients.

The above-mentioned epidemiological studies indicate the need to carry out further methodologically relevant research on the underlying pathogenetic basis of the described comorbidities. The institution of screening tests for PCOS patients seems essential, especially in the context of depression, anxiety disorders and eating disorders, in order to diagnose and potentially treat any existing comorbidities. Scheduling a routine consultation by a psychologist, especially in newly diagnosed PCOS patients, might be a beneficial first step in identifying potential psychiatric disorders. If indicated, subsequent psychiatric consultations could be scheduled. Implementing such practices could provide a more comprehensive approach to treating patients with polycystic ovary syndrome.

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Address: Agnieszka Remlinger-Molenda
Department of Adult Psychiatry, Poznan University of Medical Sciences
60-572 Poznań, Szpitalna Street 27/33
e-mail: aremlinger@gmail.com