Neuroendocrine, neurotransmitter, and gut microbiota imbalance contributing to potential psychiatric disorder prevalence in polycystic ovarian syndrome

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Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women, affecting up to 15% of reproductive-aged women. Polycystic ovarian syndrome is a heterogeneous disorder, both in the sense that many different factors may play a role in its manifestation and that multiple systems throughout the body can be affected. Polycystic ovarian syndrome has been linked to an increased prevalence of various psychiatric disorders, including depression and anxiety. Despite the socioeconomic effect that these disorders may have on patients with PCOS and society as a whole, this association is largely lacking in research. There are currently several theories regarding the link between PCOS and mental health. Some suggest that the overactive hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axes in PCOS patients may alter the hormonal profile and contribute to the development of psychiatric disorders. Other studies speculate that abnormal levels of neurotransmitters and neuronal signaling may play a role. Recently, more research has begun to focus on the gut-brain axis, addressing the nutritional needs of PCOS patients. Studies show that dietary factors such as probiotics and micronutrient supplementation may significantly improve psychiatric symptoms in PCOS patients while helping regulate neurotransmitter levels in the body. In this review, we examine different theories regarding the association between PCOS and psychiatric disorders and point out different areas of research that are needed to broaden our understanding of this association. (Fertil Steril Rep® 2023;4:337–42. ©2023 by American Society for Reproductive Medicine.)

Key Words: Gut-brain axis, neuroendocrine effects, neurotransmitter effects, polycystic ovarian syndrome, psychiatric disorders

Polycystic ovarian syndrome (PCOS) affects a large population of women worldwide. It is estimated that up to 15% of reproductive-aged women are affected by PCOS, and it is a complex condition that often goes undiagnosed (1, 2). Polycystic ovarian syndrome is diagnosed following criteria set by the National Institute of Health if at least two of the following symptoms are present: irregular menses, polycystic ovaries, and hyperandrogenism (1–3). Symptoms of PCOS may manifest before or during the first menstrual cycle, although the diagnosis is not usually made until later in life (1).

Polycystic ovarian syndrome is highly associated with gynecologic, metabolic, and endocrine dysfunction, which can lead to a wide variety of clinical manifestations, including hirsutism, oligomenorrhea, infertility, and insulin resistance (1–2). Therefore, it is important for healthcare providers to evaluate and treat PCOS patients from multiple approaches. Although mental illnesses are known to be associated with PCOS, they are often undiagnosed and undertreated. Several commonly observed psychiatric disorders are associated with PCOS, including depression, generalized anxiety disorder, social phobia, attention deficit hyperactivity disorder, and obsessive-compulsive disorder (4). Psychiatric disorder presentation is associated with neuroendocrine and neurotransmitter dysfunction but may also be a result of altered hormones and even diet (5–8).

In this review, we discuss systemic changes in PCOS that may lead to an increased prevalence of psychiatric disorders, focusing specifically on neuroendocrine, neurotransmitter, and gut-brain dysfunction. Despite the

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socioeconomic effect that psychiatric disorders have on individual patients with PCOS and our society as a whole, this area is largely lacking in research.

NEUROENDOCRINE EFFECTS IN PCOS

Two major regulatory pathways of the neuroendocrine system are the hypothalamic-pituitary-ovarian (HPO) and hypothalamic-pituitary-adrenal (HPA) axes. In the HPO axis, gonadotropin-releasing hormone (GnRH) release from the hypothalamus controls the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland. The GnRH modulates the amount and rate of LH and FSH production. The LH and FSH then act to regulate ovarian androgen and estrogen production. In PCOS, the GnRH pulse generator is abnormal, leading to an abnormal LH and FSH secretion. This neuroendocrine dysregulation and the resulting effects of downstream hormonal signaling may then contribute to the manifestation of psychiatric disorders. More specifically, studies show that women with PCOS have an increased LH pulse frequency, LH pulse amplitude, and LH/FSH ratio (9, 10). This imbalance contributes to the excessive androgen production that is characteristic of PCOS, leading to impaired hypothalamic-pituitary feedback over time and further dysregulation. Even though PCOS is typically associated with estrogen-dominant conditions such as endometrial hyperplasia because of chronic anovulation, average estrogen levels may be lower overall in some patients because of lack of ovulation and development of a dominant follicle. Therefore, it is possible that PCOS patients may paradoxically be at risk of some sequelae of estrogen deficiency. Estrogen-deficient states such as menopause have been associated with a higher risk of developing psychosis and psychotic disorders, such as schizophrenia (6). Estrogen replacement has even been shown to reduce psychotic symptoms in some patients with schizophrenia (6). Furthermore, studies show that women with psychotic disorders exhibit PCOS-like symptoms such as menstrual irregularity (6).

Hormonal imbalances in PCOS, such as hyperandrogenism, lead to the classic phenotype of enlarged ovaries with a string-of-pearl morphology and theca interstitial hyperplasia (2). However, the effects of hyperandrogenism are not limited to the ovaries. Systemic effects of excess androgens include acne, hirsutism, and male-pattern hair loss, as well as psychiatric symptoms. Studies have shown that hyperandrogenism is significantly associated with higher depression scores in older women with PCOS (11). Additionally, women diagnosed with both PCOS and anxiety have been found to have higher levels of free testosterone than women with PCOS only (11).

Although the HPO axis plays a key role in regulating the production of testosterone and androstenedione, the HPA axis is largely responsible for dehydroepiandrosterone (DHEA) production by the adrenal gland. DHEA is a precursor hormone that is synthesized from cholesterol in the adrenal cortex and is then converted to active androgens and estrogens peripherally. The majority of circulating DHEA exists as DHEA sulfate (DHEA-S) once released from the adrenal cortex. It is estimated that 20 to 30% of women with PCOS have elevated levels of DHEA-S (12).

Elevated DHEA levels have been associated with the development of neuropsychiatric disorders. High androgen levels can cause serious psychological effects arising from changes in preexisting psychiatric disorders. In a study by Balikci and coworkers (13), serum hormone levels and psychiatric metrics were compared between women with and without PCOS. The results show that the group with PCOS had higher levels of DHEA-S and total testosterone, as well as higher scores of anxiety, depression, and anger. The authors also reported a significant positive relationship between anxiety scores and serum DHEA-S levels in all subjects, possibly related to the gamma-aminobutyric acid (GABA)-antagonistic effect of DHEA-S. On the other hand, there was no relationship between depression and DHEA-S, suggesting that depressive symptoms may be secondary to distressing symptoms such as hirsutism or infertility.

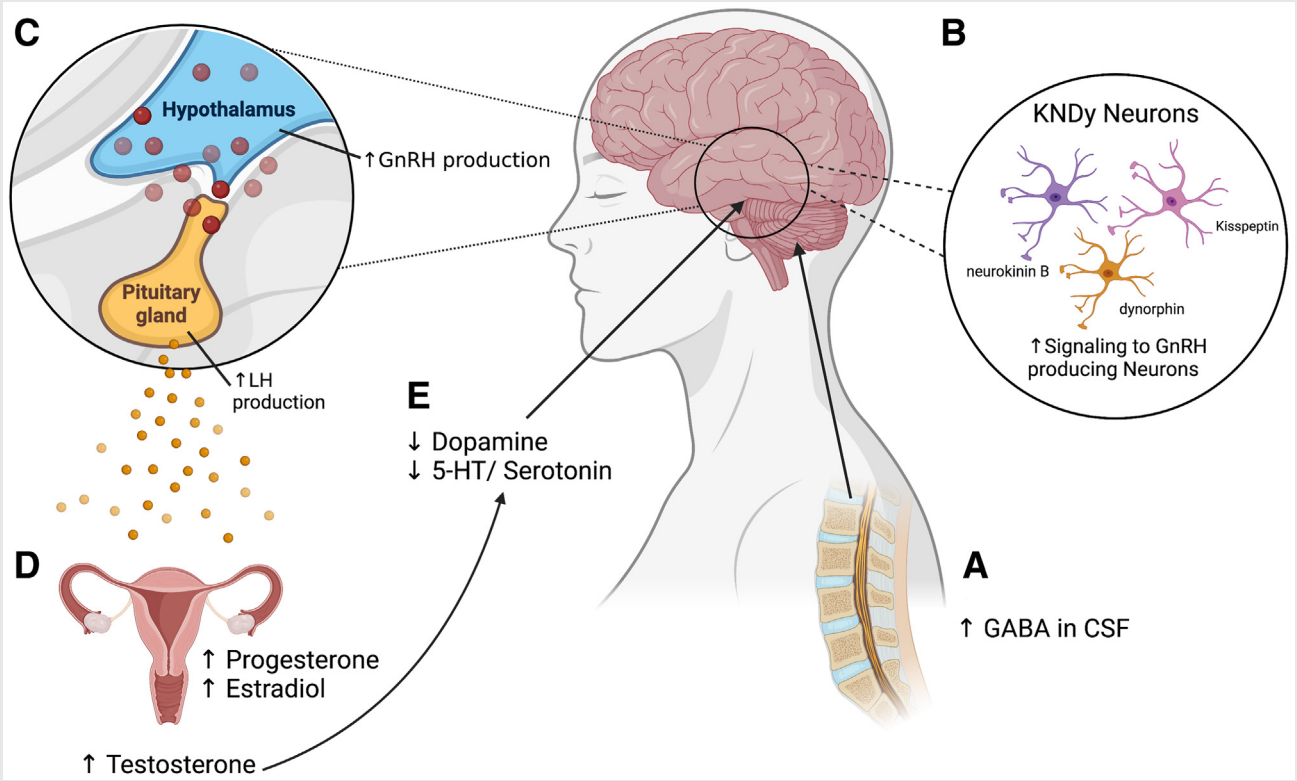
The HPA axis is an essential component of the stress response, but there are many other structures that play a role as well. The amygdala is a gray matter structure in the bilateral medial temporal lobes that is activated during the processing of fearful stimuli. The amygdala stimulates brainstem neurons, acting to inhibit the parasympathetic nervous system and excite the sympathetic nervous system, which results in the release of epinephrine and norepinephrine (NE). At the same time, the amygdala also excites a group of neurons in the paraventricular nucleus of the hypothalamus. These neurons increase the production of cortisol-releasing hormone from the base of the hypothalamus, which regulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. The ACTH then acts on the adrenal glands to increase glucocorticoid secretion. Patients with PCOS have been found to have an overactive HPA axis and, thus, excessive cortisol production, leading to physiologic anxiety and stress response (14).

The typical response to the sudden increase in glucocorticoids and sympathetic nervous system activity is known as a "fight or flight" response and involves a sharp increase in blood pressure and heart rate (15). Patients with mood disorders may experience chronically elevated serum cortisol levels, which disrupts multiple bodily functions related to the acute stress response (15). Furthermore, menstrual irregularities and hyperandrogenism are commonly observed in patients with chronic anxiety, similar to the presentation of PCOS.

EFFECT OF NEUROTRANSMITTERS IN PCOS

Neurotransmitters are signaling molecules released at neuronal synapses that are essential for the regulation of numerous bodily functions. The development of psychiatric illnesses has largely been attributed to abnormal levels of neurotransmitters and aberrant neuronal signaling pathways. Likewise, neurotransmitter dysregulation is commonly observed in patients with PCOS and neuropsychiatric disorders (3). The arcuate nucleus of the hypothalamus (ARC) is known to regulate hunger, metabolism, and the onset of puberty. One group of neurons in the ARC secretes the neuropeptides kisspeptin, neurokinin B, and dynorphin; this group is named the KNDy neuropeptides. As seen in

FIGURE 1



Neurotransmitter and neuropeptide relationships with the HPO axis in PCOS. (A) Patients with PCOS sometimes have higher levels of GABA found in cerebrospinal fluid. These high levels cause dysfunctional GABAergic neurons, which can regulate anxiety and fear. (B) The high levels of GABA being secreted cause the dysfunction of KNDy neurons, which are commonly found centrally in the brain. The altered signaling of these neurons causes the hypothalamus to start producing more GnRH. (C) The increase of GnRH increases the secretion of LH. (D) Increased LH upregulates the production of progesterone, estradiol, and testosterone. (E) The abnormal increase in testosterone decreases dopamine and serotonin levels in the bloodstream and the brain (2, 3, 14).

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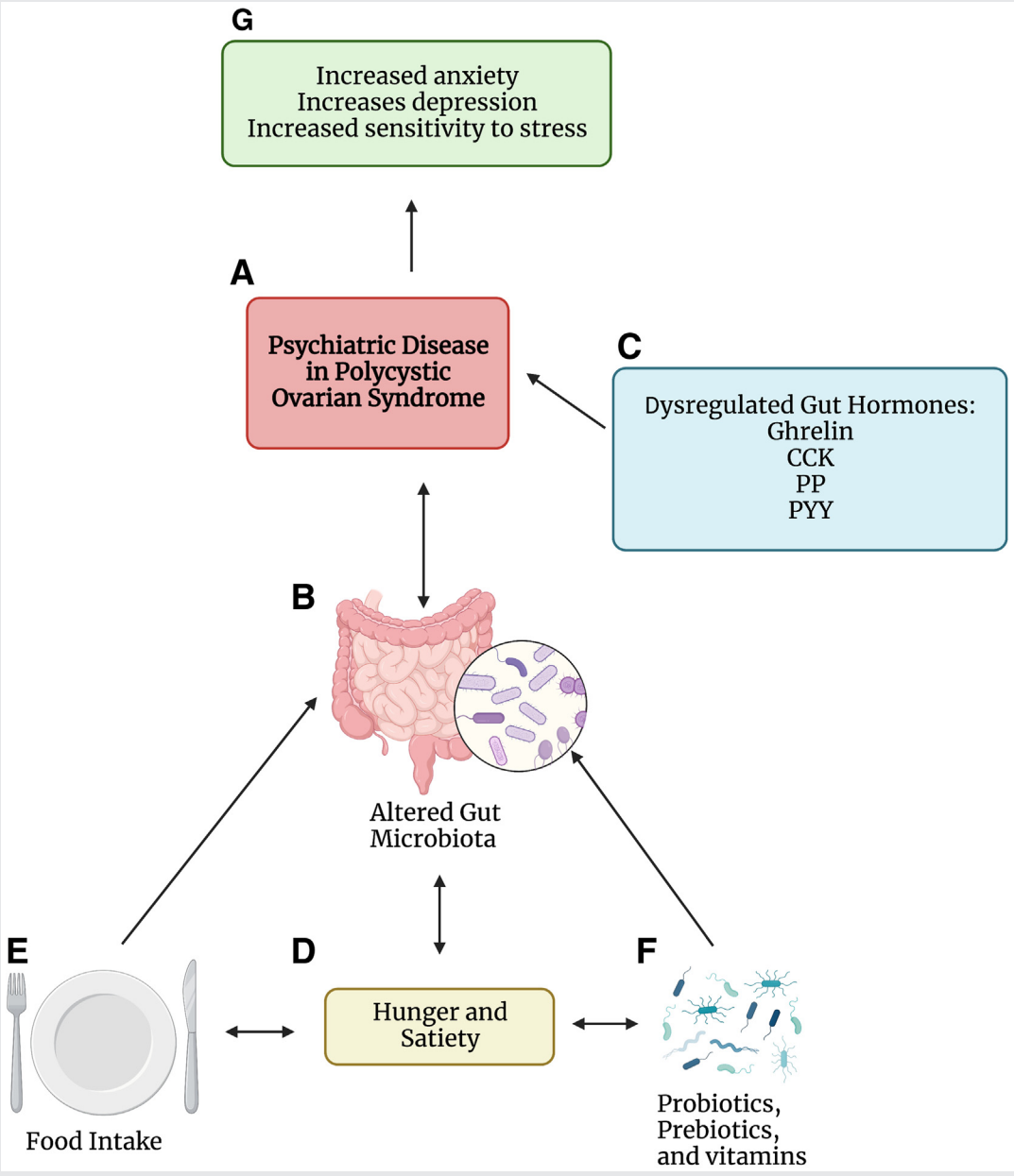
Figure 1, the KNDy neuropeptides activate the GnRH pulse generator in the hypothalamus in response to hormonal inputs and sufficient deactivation of inhibitory inputs. Thus, ARC acts as a direct upstream regulator of GnRH release from the hypothalamus (2, 3, 14). In patients with PCOS, it has been proposed that abnormal levels of neuropeptide signaling from the ARC are a driving force of GnRH dysregulation. In addition, studies show that abnormal KNDy neuropeptide production may have a substantial psychiatric effect, as the three neuropeptides all function as regulators of neuroendocrine processes that affect behavior and mood (2, 3, 14).

Apart from this group of neuropeptides, monoamine neurotransmitters have also been implicated in the relationship between PCOS and neuropsychiatric disorders. Monoamine neurotransmitters, such as serotonin (5-hydroxytryptamine [5-HT]), NE, and dopamine (DA), are widely produced throughout the central nervous system and are involved in a wide range of functions, including learning, emotion, and memory. Norepinephrine, 5-HT, and DA signaling has been found to play a central role in the development of many psychiatric disorders, including depression, anxiety, obsessive-compulsive disorder, and schizophrenia. Furthermore, they affect the regulation of GnRH release and may, thus, play a role in the PCOS disease pathway. Studies show that NE and epinephrine levels are significantly decreased in the hypothalamus and pituitary glands of PCOS animal models (16). Low levels of NE and epinephrine may result in symptoms of anxiety, depression, and chronic stress (8). This finding may help explain the linkage between PCOS and psychiatric diseases.

Similarly, research shows that DA and 5-HT signaling may also be implicated in that relationship. Dopamine is a neurotransmitter that is known to regulate the brain's pleasure and reward systems. It also acts as a suppressor of the GnRH release pathway and is generally lower in patients with PCOS (8). Low levels of DA have been associated with increased fatigue, stress, and depressed mood. In addition, newer studies suggest that 5-HT may also modulate GnRH release, although the exact mechanism is unclear (16). The 5-HT imbalance is a widely accepted driver of mood disorders, and serotonin reuptake inhibitors are the first-line treatment for depression and anxiety. In animal models of PCOS, 5-HT has been shown to be decreased in the hypothalamus and pituitary glands. Sex hormones have been linked to 5-HT signaling in humans, with some research showing

FIGURE 2



Gut-brain connection in PCOS. (A) PCOS is central to illustrating its interactions with the GI tract. (B) Gut bacteria levels can be abnormal in PCOS and can contribute to PCOS. (C) These hormones can cause PCOS and PCOS-like symptoms. (D) Hunger and satiety affect the voluntary intake of nutrients into the body. (E) The type and amount of food consumed. (F) Microbiota and dietary supplements added to a diet impact preexisting microbiota in the gut. (G) The result of PCOS being unmanaged and the development of psychiatric disease (19, 22).

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that testosterone therapy alters the availability of 5-HT receptors in the brain (16). Testosterone therapy has been successfully used to treat mood symptoms in some patients, although further research is needed to elucidate the exact mechanism. Nevertheless, chronically elevated androgen levels in women with PCOS may be significantly altering 5-HT signaling in the brain and increasing the propensity for mood disorders.

GUT-BRAIN PATHWAYS IN PCOS

Recently, the clinical view of PCOS has shifted from a purely gynecologic and endocrine condition to a multisystem disease (8). One system that has gained more attention is the gastrointestinal (GI) system. The hypothalamus is a major regulator of GI functions such as digestion, metabolism, and appetite, and PCOS has been shown to affect this relationship. Furthermore, the GI tract has been recognized as a peripheral secretor

of hormones and neurotransmitters that directly affect the central nervous system. Therefore, the altered gut-brain axis in patients with PCOS is thought to contribute to the development of GI and psychiatric manifestations through dysregulation of gut hormones and other signaling molecules as well as the gut microbiome (8, 17, 18).

As much as the brain regulates appetite and food intake, the inverse has also been found to be true. Dietary factors can significantly impact mood, and certain dietary changes may help with mood regulation. On the other hand, nutrition deficiencies have been linked to the manifestation of neuropsychiatric disorders (19). The micronutrient requirements of the human body have been extensively studied, and it is widely known that insufficient intake of certain vitamins or minerals can cause symptoms such as immune dysfunction or memory loss.

Recent research shows that micronutrient and probiotic supplementation may be linked to PCOS and mood disorders. One study aimed to assess the effects of vitamin D and probiotic administration on various biological parameters and subject-reported metrics related to depression, anxiety, and stress in women with PCOS. Ostadmohammadi et al (19) reported that after 12 weeks, the group with vitamin D and probiotic treatment showed significantly improved mental health parameters in comparison to the control group. They also found reductions in serum testosterone, hirsutism, and CRP levels. Similar results were seen in other studies involving probiotic and selenium supplementation (20). These findings are particularly significant because PCOS has not been previously studied with regard to nutritional supplementation.

Further evidence also supports the idea that the gut microbiome plays a crucial role in the regulation of the gut-brain axis and can modulate the release of neurotransmitters and other signaling molecules. Gamma-aminobutyric acid is a major inhibitory neurotransmitter that has been implicated in psychiatric disorders such as anxiety. Certain strains of gut bacteria that have been shown to alter GABA concentrations in cerebrospinal fluid have been found in higher quantities in PCOS patients, supporting the idea that the gut-brain axis contributes to the linkage between PCOS and psychiatric disease (3).

Various gut hormones are known to have an effect on mood symptoms and the development of neuropsychiatric disorders. As discussed above, the production of these hormones is partially controlled by the hypothalamus and pituitary gland, which are dysregulated in PCOS. Women with PCOS have been shown to have increased ghrelin, decreased cholecystokinin, and decreased peptide YY production (Figure 2). Peptide YY is part of a group of biologically active peptides known as the neuropeptide Y (NPY) family, which also includes NPY and pancreatic polypeptide. The NPY family is crucial to the regulation of energy homeostasis, mood, anxiety, and stress tolerance. These peptides are produced at various levels along the gut-brain axis, including peripherally by endocrine cells in the GI tract and centrally throughout the brain, and act on many receptor types. The NPY is the most abundant neuropeptide in the brain and is found in multiple brain regions, including the hypothalamus, hippocampus, amygdala, basal ganglia, cerebral cortex, and medulla. Its ubiquity throughout the brain allows this neuropeptide to have a wide range of effects (8, 17, 21). Animal experiments suggest that NPY is involved in the stress response and may have an anxiolytic effect (8). It has also been observed that peptide YY and pancreatic polypeptide both act to decrease depressive symptoms in patients with psychiatric disorders, and cholecystokinin has been found to increase anxious behaviors at abnormal levels (8, 17, 21).

Another important regulator of the gut-brain axis is ghrelin. Although ghrelin is primarily known for its role as the "hunger hormone," it has many other actions as well. The hypothalamus is its primary site of action, once again linking this hormone with the PCOS disease process. Additionally, ghrelin has been found to influence neurotransmitter release and gene expression throughout other brain regions. Research has shown that ghrelin helps regulate the activity of the HPA axis, specifically by modulating ACTH and cortisol secretion (8). Ghrelin may also have a role in the activation of the cholinergic-dopaminergic reward link, thus affecting processes such as motivation, goal setting, and reward. In this way, ghrelin may also affect the actions of DA-producing neurons in the brain.

CONCLUSIONS

It is essential to note that each system discussed in this review is interconnected in the sense that small alterations in one system may significantly affect the functioning of another. Because PCOS is a multisystem disease, it is important to study it as such. For example, neurotransmitters such as DA and NE may act as mood regulators in the brain, but they can simultaneously contribute to the regulation of appetite and satiety and influence the gut-brain axis. Ultimately, it is crucial to study each of these interactions to advance our understanding of PCOS.

The relationship between PCOS and psychiatric disease may substantially affect the quality of life in patients with PCOS, as well as their response to treatment. For this reason, it is imperative for healthcare providers to be aware of this linkage. This review highlights the central multisystemic aspects of PCOS, specifically in regard to the development and manifestations of psychiatric diseases. It is clear that further research is needed to broaden our understanding of how exactly these various systems are intertwined. Beyond scientific knowledge, it is also vital that patients have access to a comprehensive understanding of their disease and the resources available to them. Increased awareness may also lead to new treatment options and preventive education among at-risk groups.

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REFERENCES

1. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.

2. Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc 2019;3:1545–73.
3. Szeliga A, Rudnicka E, Maciejewska-Jeske M, Kucharski M, Kostrzak A, Hajbos M, et al. Neuroendocrine determinants of polycystic ovary syndrome. Int J Environ Res Public Health 2022;19:3089.
4. Rodriguez-Paris D, Remlinger-Molenda A, Kurzawa R, Głowińska A, Spaczyński R, Rybakowski F, et al. Psychiatric disorders in women with polycystic ovary syndrome. Psychiatr Pol 2019;53:955–66.
5. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ, Moran LJ. Depression, anxiety and perceived stress in women with and without PCOS: a community-based study. Psychol Med 2019;49:1510–20.
6. Doretto L, Mari FC, Chaves AC. Polycystic ovary syndrome and psychotic disorder. Front Psychiatry 2020;11:543.
7. Hung JH, Hu LY, Tsai SJ, Yang AC, Huang MW, Chen PM, et al. Risk of psychiatric disorders following polycystic ovary syndrome: a nationwide population-based cohort study. PLoS One 2014;9:e97041.
8. Ilie IR. Neurotransmitter, neuropeptide and gut peptide profile in PCOS-pathways contributing to the pathophysiology, food intake and psychiatric manifestations of PCOS. Adv Clin Chem 2020;96:85–135.
9. Esparza LA, Schafer D, Ho BS, Thackray VG, Kauffman AS. Hyperactive LH pulses and elevated kisspeptin and NKB gene expression in the arcuate nucleus of a PCOS mouse model. Endocrinology 2020;161:bqaa018.
10. Chaudhari AP, Mazumdar K, Mehta PD. Anxiety, depression, and quality of life in women with polycystic ovarian syndrome. Indian J Psychol Med 2018;40:239–46.
11. Cooney LG, Dokras A. Depression and anxiety in polycystic ovary syndrome: etiology and treatment. Curr Psychiatry Rep 2017;19:83.
12. Yildiz BO, Azziz R. The adrenal and polycystic ovary syndrome. Rev Endocr Metab Disord 2007;8:331–42.
13. Balikci A, Erdem M, Keskin U, Bozkurt Zincir S, Gülsün M, Özçelik F, et al. Depression, anxiety, and anger in patients with polycystic ovary syndrome. Noro Psikiyatr Ars 2014;51:328–33.
14. Moore AM, Campbell RE. Polycystic ovary syndrome: understanding the role of the brain. Front Neuroendocrinol 2017;46:1–14.
15. Sapolsky RM. Behave: The biology of humans at our best and worst. Penguin Press; 2017.
16. Chaudhari N, Dawalbhakta M, Nampoothiri L. GnRH dysregulation in polycystic ovarian syndrome (PCOS) is a manifestation of an altered neurotransmitter profile. Reprod Biol Endocrinol 2018;16:37.
17. He FF, Li YM. Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: a review. J Ovarian Res 2020;13:73.
18. Liang Z, Di N, Li L, Yang D. Gut microbiota alterations reveal potential gut-brain axis changes in polycystic ovary syndrome. J Endocrinol Invest 2021;44:1727–37.
19. Ostadmohammadi V, Jamilian M, Bahmani F, Asemi Z. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. J Ovarian Res 2019;12:5.
20. Jamilian M, Mansury S, Bahmani F, Heidar Z, Amirani E, Asemi Z. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. J Ovarian Res 2018;11:80.
21. Katulski K, Podfigurna A, Czyzyk A, Meczekalski B, Genazzani AD. Kisspeptin and LH pulsatile temporal coupling in PCOS patients. Endocrine 2018;61:149–57.
22. Liu Y, Qi Q. ROC curve in evaluation of diagnostic value of serum 25-hydroxyvitamin-D for PCOS with depression. J Coll Phfysicians Surg Pak 2020;30:659–61.