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VALPROATE, BIPOLAR DISORDER AND POLYCYSTIC OVARIAN SYNDROME

VALPROAT, BIPOLARNI POREMEĆAJ I SINDROM POLICISTIČNIH JAJNIKA

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Summary

Introduction. Polycystic ovarian syndrome is a syndrome of ovarian dysfunction with the principal features of hyperandrogenism and polycystic ovary morphology. A large number of studies conducted on this topic have suggested a possible role of anticonvulsants, particularly valproate, in the pathogenesis or risk factors associated with polycystic ovarian syndrome. Bipolar treatment guidelines from Canada and the United States of America recommend valproate as the first line strategy in the acute treatment of bipolar disorder. **Discussion.** Most persons with bipolar disorder require maintenance treatment. Long-term administration of valproate in women with bipolar disorder or epilepsy is believed to result in the increased risk of hyperandrogenism, menstrual abnormalities and polycystic ovaries. Valproate may also increase the risk of infertility and other associated symptoms of polycystic ovarian syndrome. Therefore, particular caution is indicated in the use of valproate in women of reproductive age. **Conclusion.** The treatment of the female patients with bipolar disorder presents various challenges for the clinician. Every woman of reproductive age needs to know the risk and benefits of her pharmacologic treatment options. Bipolar disorder should be considered chronic disorder, whose development is largely affected by hormonal changes and reproductive cycle in women. These issues should be researched more thoroughly in order to opt for the most appropriate treatment in women with bipolar disorder.

Key words: Polycystic Ovary Syndrome; Bipolar Disorder; Epilepsy; Valproic Acid; Risk Factors; Anovulation; Menstrual Cycle; Gonadal Hormones; Obesity; Hyperandrogenism

Introduction

Since polycystic ovary syndrome (PCOS) affects 2-7% of women of reproductive age, it ranks among the most common endocrine disorders. PCOS is characterized by both hormonal and metabolic disorders, and the disorder itself could be characterized as hyperandrogenism and chronic anovulation in

Sažetak

Uvod. Sindrom policističnih jajnika je ovarijalna disfunkcija čije su osnovne karakteristike hiperandrogenizam i policistična struktura jajnika. Veliki broj do sada sprovedenih studija ukazuje na moguću ulogu antikonvulzivnih lekova, prevashodno valproata, u patogenezi sindroma policističnih jajnika ili je primena valproata još jedan faktor rizika u razvoju pomenutog sindroma. **Smernice** za lečenje bipolarnog poremećaja iz Kanade i Amerike preporučuju valproat kao lek prvog izbora u akutnom tretmanu bipolarnog poremećaja. **Diskusija.** Veliki broj osoba sa bipolarnim poremećajem zahteva tretman održavanja. Smatra se da produžena terapija valproatom kod žena obolelih od bipolarnog poremećaja i epilepsije doprinosi povećanom riziku od pojave hiperandrogenizma, poremećaja menstrualnog ciklusa i sindroma policističnih jajnika. Valproat takođe može povećati rizik od neplodnosti i drugih simptoma udruženih sa sindromom policističnih jajnika. Iz ovih razloga potreban je poseban oprez ukoliko se valproat upotrebljava u periodu reproduktivnih godina žene. **Zaključak.** Tretman žena obolelih od bipolarnog poremećaja predstavlja veliki izazov za kliničare. Svaka žena u reproduktivnim godinama mora biti upoznata sa koristima i potencijalnim rizicima od upotrebe različitih farmakoterapijskih mogućnosti u lečenju bipolarnog poremećaja. Bipolarni poremećaj je potrebno posmatrati kao hronični poremećaj na čiji tok u velikoj meri utiču hormonske promene i reproduktivni ciklus kod žena. Neophodna su dalja istraživanja ove teme kako bi se obezbedio najadekvatniji tretman ženama obolelim od bipolarnog poremećaja. **Ključne reči:** Sindrom policističnih jajnika; Bipolarni poremećaj; Epilepsija; Valproična kiselina; Faktori rizika; Anovulacija; Menstrualni ciklus; Polni hormoni; Gojaznost; Hiperandrogenizam

the absence of the pituitary and adrenal pathology. Given that PCOS is defined as a clinical syndrome, no diagnostic criterion is sufficient for clinical diagnosis [1].

Polycystic ovary syndrome is characterized by co-occurrence of increased androgen levels and menstrual cycle disorder. Androgens are subject to aromatization in fatty tissue. The product of this aroma-

Abbreviations

PCOS	– polycystic ovary syndrome
LH	– luteinizing hormone
FSH	– follicle-stimulating hormone
GnRH	– gonadotropin-releasing hormone
IGF-1	– insulin-like growth factor
VPA	– valproate
CYP	– cytochrome P450 oxidase
AAPs	– atypical antipsychotics

tization, which is referred to as extraglandular, is *estrone*. A characteristic of this weak estrogen is to sensitize the pituitary gland, produce luteinizing hormone (LH) intensively under the influence of gonadotropin-releasing hormone (GnRH), while on the other hand hindering it in the creation of follicle-stimulating hormone (FSH). The high level of LH stimulates the cells of the stroma and theca to produce androgens, mainly *androstenedione* and *testosterone*. These androgens join the adrenal androgens thus closing the circle from which there is no spontaneous escape. A consistently low level of FSH continuously stimulates the development of follicles, which are subject to atresia, because it is insufficient for their proper growth and maturation. The end result is anovulation with other clinical manifestations, such as acne and hirsutism.

Although the etiology of PCOS is not determined and defined in a satisfactory way, there has recently been more and more data pointing to insulin resistance as an important component. Hyperinsulinemia is a side effect of peripheral insulin resistance (a probable absence or blockage of the insulin receptors), and this phenomenon is also known to be more common in obese patients. Insulin, which is excessive and does not find its receptors, binds to insulin-like growth factor (IGF-1) receptors, which are structurally similar to insulin receptors. Since IGF-1 is known to make theca cells particularly sensitive to the effects of LH, it is clear then that the ovaries of these patients are the major source of androgens. Furthermore, insulin has inhibitory effect on the synthesis of sex hormone-binding globulin (SHBG) in the liver; hence free androgens in serum further deteriorate the patient's condition [2].

Elevated concentrations of insulin may initiate a cascade of events which may eventually result in metabolic syndrome. Metabolic syndrome is a collection of physical symptoms and signs that represent the most important risk factors for cardiovascular and cerebrovascular diseases, and it includes obesity, diabetes mellitus type II, hypertension, hypertriglyceridemia and low levels of high-density lipoprotein (HDL) cholesterol [3].

Bipolar treatment guidelines from Canada and the United States of America recommend valproate as the first line strategy in the acute treatment of bipolar disorder [1]. A large number of studies conducted so far suggest a possible role of anticonvulsant drugs (primarily VPA) in the pathogenesis of PCOS in patients suffering from bipolar disorder

and epilepsy. These studies found an association between the long-term application of VPA and an increased risk of hyperandrogenism and menstrual cycle disorders and the consequent development of PCOS [4]. Higher prevalence of overweight or obesity was also detected among women suffering from bipolar disorder compared to the general population. Adverse effect of VPA in the form of an increase in body weight has long been proven. Obesity itself may predispose or be one of the risk factors in the development of numerous endocrine and metabolic disorders including PCOS, which in addition to the previously mentioned, results in infertility due to anovulation. Given that VPA may increase the risk of infertility causing PCOS, it is necessary to be particularly careful when applying it in the treatment in women of reproductive age suffering from bipolar disorder [5].

This paper has been aimed at reviewing the current literature that examines the association between bipolar disorder, administration of VPA and the subsequent development of PCOS in order to provide women suffering from bipolar disorder the most optimal treatment. To achieve this, the impact of endocrine and reproductive events on the course of the disorder, as well as the implications of psychiatric treatments upon the course of reproductive events must be understood.

Discussion

A large number of studies conducted on the association between bipolar disorder, application of VPA and the occurrence of PCOS have found a higher prevalence of PCOS in women suffering from bipolar disorder [6]. The theories which tried to explain this increased prevalence included the effects of PCOS or effects of the application of VPA that could cause the development of PCOS directly or indirectly. Metabolic disorders were confirmed both in patients suffering from bipolar disorder and in those suffering from PCOS. Insulin resistance, hyperglycemia and obesity are common to patients suffering from both bipolar disorder and PCOS, thus suggesting that there is a certain degree of pathophysiological overlap between these two disorders. Due to the fact that both bipolar disorder and PCOS are complex polygenetic diseases, endophenotypic overlap between these two disorders may be a result of common genes. Future studies to be conducted on this issue should provide definitive confirmation of genetic overlap between these two disorders [7].

Studies that compared the long-term use of lithium as opposed to long-term treatment with VPA in women suffering from bipolar disorder pointed to a significantly higher rate of menstrual cycle disorders in patients receiving prolonged VPA therapy compared to women who had been treated with lithium for a long time [1]. The increased rate of hyperandrogenism and development of the metabolic syndrome was also confirmed in women

treated for long time with VPA compared to long-term treatment with lithium [8].

The most frequently cited mechanisms of impact of VPA on the development of PCOS are:

1. Increased androgen synthesis in the ovaries
2. Impact of GnRH on intensive production of LH
3. Increase in body weight and insulin resistance
4. Absence of induction of hepatic microsomal enzyme cytochrome P450 oxidase (CYP)
5. Use in vulnerable populations (e.g. patients suffering from epilepsy, young people, irregular menstrual cycles)

Preliminary data suggest a possible direct effect of VPA on an increased androgen production in the ovaries, but there is still no reliable evidence of its influence on the development of the symptoms of PCOS. The manner in which VPA potentially achieves a direct effect on the ovaries is the impact on GnRH which stimulates the intensive production of LH resulting in increased ovarian androgens synthesis - mainly testosterone [9].

The risk of overweight and obesity was higher in women with bipolar disorder than in the healthy controls, whereby psychopharmaceuticals used in the treatment of bipolar disorder increased central obesity, and thus contributed to the increased cardiovascular morbidity [10]. The increase in body weight may impair the compliance and the positive doctor – patient relationship, and also lead to a number of other medical complications such as high blood pressure, high triglycerides, diabetes, etc. The increase in body weight may potentially cause an increased risk of PCOS, probably because overweight causes the development of insulin resistance [11]. It has been found that women treated with VPA are more likely to be obese than women treated with some other mood stabilizers used in the treatment of bipolar disorder [12]. Loss of body weight after discontinuation of VPA has contributed to the improvement of the symptoms of PCOS which could indicate that obesity may increase the risk of developing PCOS. In case reports on this subject, the replacement of VPA with lamotrigine resulted in a decline in serum testosterone levels with improved ovarian ultrasonographic findings in the following period [13]. It was also shown that the women who had developed obesity with amenorrhea while being treated with VPA, lost weight after replacing the above psychostabilizers (VPA replaced by lamotrigine) with the re-stabilization of the menstrual cycle [14]. Being an adverse effect of the application of VPA, obesity may potentiate the development of symptoms of PCOS; therefore, many authors advise regular monitoring of body weight and prevention of obesity as a risk factor in the possible development of PCOS [15].

Apart from leading to an increase in body weight and elevated insulin levels in the blood, VPA also contributes to the increased concentration of leptin in the blood. Leptin, a peptide synthesized primarily by the adipocytes, acts at the level of the hypothalamus modulating the neuroendocrine axis, energy expenditure and appetite. Leptin levels correlate with

the body mass index (BMI) and may reflect the size of the peripheral adipose depot. Elevated leptin levels may be a critical effector system in the initiation of reproductive hormone changes [1].

A pharmacodynamic property of VPA that might contribute to an association with PCOS is its lack of induction of hepatic microsomal CYP oxidases (contrary to barbiturates, carbamazepine and phenytoin). The induction of CYP isoenzymes facilitates clearance of gonadal steroids and reduces the circulating testosterone levels. Since VPA does not induce CYP enzymes, it lacks this mitigating action against hyperandrogenemia – an action that might otherwise limit the risk of PCOS indirectly [9].

If the administration of VPA contributes to the risk for PCOS, it is possible that the effect may be seen only in the women who already have other risk factors for this disorder, such as epilepsy, obesity, or preexisting PCOS morphology. Women with epilepsy may be particularly susceptible to PCOS because they have high rates of anovulatory cycles, reproductive-endocrine disorders, and neuroendocrine abnormalities, such as altered release of GnRH and LH [16]. Based on the above mentioned findings, it has been concluded that reproductive disorders in women suffering from epilepsy may be caused by the use of anticonvulsant medications as well as by neuroendocrine effects induced by the disease itself [17]. The situation is similar in women with bipolar disorder because the neuroendocrine system plays a central role both in disorders of the reproductive function and the occurrence of mood disorders.

Women with bipolar disorder are often treated with combinations of psychotropic medications including atypical antipsychotics (AAPs), a class of medication that has been associated with weight gain, central adiposity, and the development of insulin resistance and type 2 diabetes. All of these side effects can be potential risk factors in the development of PCOS symptoms [18].

A meta-analysis of 11 studies performed on a sample of 556 women with epilepsy treated with VPA, 593 women treated with some other anticonvulsant, 120 women in whom epilepsy was not treated and 329 healthy controls showed an increased incidence of PCOS in the women treated with VPA compared to the women who did not use VPA. The results differed because of various definitions of the diagnostic criteria for PCOS. Treatment with VPA was associated with an increased incidence of PCOS in the criteria that related to hyperandrogenism, oligoovulation with two of the following three conditions fulfilled: ultrasonography of polycystic ovarian structure, the increased serum testosterone levels and menstrual cycle disorder (oligo/amenorrhea). In contrast, in the criteria of PCOS that included ovulatory dysfunction (polymenorrhea, amenorrhea or oligomenorrhea), clinical and/or biochemical evidence of hyperandrogenism was not confirmed (VPA did not increase the incidence of PCOS compared to other anticonvulsants) [19].

The fact that should not be overlooked is that irregular menstrual cycle and amenorrhea may be a physiological phenomenon. Menstrual irregularities are common in the first few years after menarche but are usually transient and non-pathological. Menstrual cycles also stop during pregnancy and are suppressed during lactation. Women over 40 years of age may experience oligomenorrhea associated with the perimenopause. In athletic women or those with eating disorders or extreme stress, common pathological causes of irregular or absent menses include hyperprolactinemia and hypothyroidism. Abnormal elevation of prolactin can induce oligo/amenorrhea and galactorrhea and it is often seen if the female patients have been using certain types of antipsychotics such as risperidone. Without evaluation of other common causes of menstrual dysfunction, PCOS cannot be assumed to be the cause of menstrual irregularities [9, 20]. Clinicians who prescribe VPA should be aware of the contradictory data describing the relationship between VPA use and PCOS [21]. Since an increasing number of young patients with epilepsy or bipolar disorder are exposed to long-term VPA maintenance therapy, it is important to define any risk associated with its long-term use [22]. Definitive data on the putative association between VPA and PCOS are imperative since PCOS is associated with infertility, diabetes mellitus, and possibly cardiovascular disease and endometrial carcinoma [9]. Most authors recommend the compulsory control of symptoms of PCOS before VPA is introduced into the treatment of women of reproductive age as well as mandatory monitoring of possible development of symptoms of PCOS after the initiation of VPA therapy [23].

The female reproductive cycle greatly affects the course of bipolar disorder (menstrual cycle, childbirth, menopause, use of hormone therapy) which makes the treatment of patients suffering from bipolar disorder even more complex. A large number of women without any psychiatric disorders experience mood changes during the menstrual cycle, and according to a great number of studies, women suffering from bipolar disorder represent a particularly vulnerable population group [24]. The differences in the manifestation of bipolar disorder also depend on the gender. A higher number of depressive episodes, rapid cycling, mixed episodes as well as medical and psychiatric co-morbidity were observed in women with bipolar disorder than in men treated for the same diagnosis. In addition, antidepressant-induced rapid cycling and the risk of progressing to mania are more often described in women with bipolar disorder than in men treated for the same diagnosis [5]. Differences in the expression of side effects also vary depending on the gender (e.g., hypothyroidism, and weight gain are more often described in women treated with lithium than in men). A study conducted in 2005 which included 17 women treated with VPA, 15 women whose therapy did not include VPA (treated for the diagnosis of bipolar disorder) and 22 healthy women without any psychiatric diagnoses,

pointed to a significantly higher percentage of menstrual cycle disorders (47%) in the group of women treated with VPA than in the women not using this drug (13%) and healthy women (0%). Bipolar disorder needs to be considered a chronic disorder whose course is largely influenced by hormonal changes and the female reproductive cycle [1].

An increased rate of menstrual cycle disorders in women with bipolar disorder as well as the associated menstrual irregularities due to long-term application of VPA and the consequent increase in the level of free testosterone in the blood has been shown in numerous papers. However, no study has managed so far to compare these results with the controls. The studies to tackle this issue and menstrual cycle disorders in the future must take into account the fact that a large number of women who subjectively report oligomenorrhea or amenorrhea have two out of three, if not all three positive ovulations during the period of monitoring ovulation (provided ovulation is monitored using biochemical parameters). All these findings suggest that more objective ways of monitoring menstrual cycle and ovulation are necessary. In some studies, psychotropic drugs were not associated with biochemical markers of menstrual cycle disorders although drugs from AAP group showed a slightly higher association with the increased rate of the present or menstrual irregularities in the past [18, 25].

In summary, reports describing a relationship between VPA use and PCOS among women with either epilepsy or bipolar disorder are contradictory. There are several possible explanations for the inconsistent findings in studies investigating the relationship between VPA use and PCOS:

- small study size
- non-randomized study design
- patients' characteristics (ethnicity, body weight)

Because of all this, well-controlled, prospective, multicenter studies are needed to confirm the correlation between the use of VPA and development of PCOS (9). If women taking VPA to be treated for bipolar disorder meet two or more of the following criteria:

1. menstrual cycle disorders
2. obesity
3. hyperandrogenism (hirsutism, alopecia)
4. anovulation (infertility),

they should check the level of free testosterone in the blood. In case of elevated findings, it would be necessary to consult a gynecologist and endocrinologist [1, 26]. In women of reproductive age who are treated with VPA, the function and structure of the ovaries (ultrasound examinations) should be evaluated regularly, especially if there is a disorder of the menstrual cycle during the treatment. Because of all these findings, clinicians must inform the patients on the possibility of a disorder of the menstrual cycle and other metabolic disorders before introducing VPA into therapy [1, 27]. The increasing number of young patients who are treated long-term with VPA for bipolar disorder necessitates further research on this issue in order to clarify the relationship between

long-term administration of VPA and other mood stabilizers and potential development of metabolic and endocrine disorders. Some studies have suggested that regardless of psychopharmaceuticals used in the treatment of bipolar disorder, women suffering from bipolar disorder are more likely to have disorders related to the menstrual cycle, which would all point to the compromised hypothalamic-pituitary-gonadal axis in bipolar patients. A study conducted in female adolescents showed that the level of androgens and LH was greater in those female adolescents who were diagnosed with bipolar disorder as compared to other psychiatric disorders [28].

Considering the aforementioned, an early development of bipolar disorder may be associated with certain symptoms of PCOS. It is believed that the early exposure to VPA administration makes female adolescents increasingly susceptible to the development of PCOS as a consequence of changes at the level of hypothalamic-pituitary-gonadal axis in the early years after menarche [9, 29]. Studies on the safety and monitoring of these medications in adolescent girls have shown high probability of development of gynecologic and reproductive adverse effects [30].

The psychiatric disorders accompanied with the clinical symptoms and hormonal abnormalities are very important although underestimated aspects in PCOS. Obesity, hirsutism, acne, menstrual disturbances and infertility play important roles in decreasing the quality of life in women with PCOS [31]. The authors discuss adverse events which are often overlooked but clinicians should pay attention to them in order to preserve the patient's quality of life [32]. The safe and effective treatment of bipolar disorder requires the cooperation between medical care providers and patients, including routine discussions on therapeutic and adverse medication effects and shared decision-making regarding changes in the therapeutic regimen. Monitoring of adverse effects is an essential component of therapeutic management [33]. One must be aware of possible endocrine side effects of antiepileptic drugs because they can have a major impact on the quality of life, and are, at least partly, reversible after antiepileptic drugs discontinuation [34].

The presence of psychiatric co-morbidity has a negative influence on the outcome of PCOS and vice versa [35]. Both endocrinologists and gynecologists,

who treat PCOS patients most frequently, should be aware of the potential presence of psychiatric disorders and should have a proactive approach to the treatment of not only physical but also psychiatric co-morbidity. Timely management of psychiatric co-morbidity can improve the outcome significantly and enhance the quality of life of these patients. In fact, a multidisciplinary team approach not only involving a gynecologist and endocrinologist but also a psychiatrist would be the most optimal way to provide adequate treatment of these patients [36].

Conclusion

Patients suffering from bipolar disorder may be of different ages and each age group for itself represents an additional risk of developing certain diseases.

Treatment of bipolar disorder in women has always been, and still is a great challenge for clinicians, the more so because the female reproductive cycle makes the treatment even more complex. The course of bipolar disorder in women is greatly influenced by menstrual cycle, childbirth, menopause and use of hormone therapy. It is essential that clinicians assess the benefits and potential risks of introducing certain mood stabilizers used in the treatment of bipolar disorder, particularly in the reproductive years of women.

Co-morbidity of bipolar disorder with physical diseases is higher than in the general population (some physical diseases such as diabetes, thyroid diseases, cardiovascular diseases, dyslipidemia, obesity and others are 30-50% more common in bipolar patients than in the general population). Inadequate monitoring of bipolar disorder and associated physical conditions result in inadequate treatment of both bipolar disorder and the associated physical diseases. Additional stigma of concomitant physical diseases in patients with bipolar disorder further undermines the patient's compliance. A psychiatrist is more successful if he/she has a "broad" view of bipolar disorder and its possible effects on the physical health of bipolar patients.

The knowledge on possible co-morbid psychiatric and/or physical conditions, as well as the knowledge on the course of bipolar disorder makes the treatment of bipolar disorder far more successful.

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