

Polycystic Ovaries and Polycystic Ovary Syndrome in Epilepsy: Evidence for Neurogonadal Disease

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Polycystic ovary syndrome (PCOS) is a mysterious reproductive disorder that results in subfertility. The underlying causes are not known, and even the definition is a moving target. Women with epilepsy have features of PCOS at a higher than expected rate, and polycystic ovaries (PCO) also are present at high rates in this population. Valproate is associated with weight gain and increased androgen levels, two features of PCOS. This review proposes that epilepsy, with its known adverse effects on luteinizing hormone pulsatility, could be a cause of PCOS and that valproate could be an imitator, if not also a cause of the syndrome.

Polycystic ovaries (PCO) and polycystic ovary syndrome (PCOS) are gynecologic entities that are associated with epilepsy and epilepsy treatments. Many neurologic conditions have medical comorbidities, such as hypertension with cerebrovascular disease and autoimmune dysfunction with multiple sclerosis, but these associations are linked by etiology. What is the etiologic connection between abnormal ovaries and epilepsy? The connection seems obscure, if not absurd; however, it appears to be real. This review discusses the evidence for the connection and proposes pathophysiologic reasons for its existence.

Definitions and Prevalence in the General Population

The National Institutes of Health (NIH) criteria for PCOS requires a) the presence of ovulatory dysfunction, such as polymenorrhea, oligomenorrhea, or amenorrhea; and b) clinical evidence of hyperandrogenism or hyperandrogenemia, such as hirsutism. Other endocrinopathies must be excluded, including thyroid dysfunction, hyperprolactinemia, late-onset congenital adrenal hyperplasia, or Cushing syndrome (1). Applying the

NIH criteria to a large group ($n = 400$) of unselected premenopausal women, the cumulative prevalence of PCOS was 6.6%, including 8% for black women and 4.8% for Caucasian women. The racial difference was not significantly different (2).

PCO are defined as 10 or more subcapsular cysts, measuring 2 to 8 mm in diameter, found within an ovary that has thickened, echogenic stroma (3,4). PCO occur in 20% to 30% of premenopausal women (5) and, alone, do not indicate reproductive dysfunction. PCO is a finding that is on the spectrum of PCOS-like reproductive dysfunction, however. For example, in a case-control study of fertility in women with PCO, the concurrent presence of any PCOS symptom, such as obesity, hirsutism, acne, or menstrual disturbances, was associated with a 2.5 to 5 times longer time to pregnancy than that in women with normal ovaries (6). Only 35% of the 258 cases of women with PCO did not have at least one PCOS symptom. Therefore, although PCO are not independently a predictor of subfertility, they are associated with the risk of subfertility in women who have other signs and symptoms of PCOS, if not the fully characterized syndrome.

The relevance of PCO to reproductive dysfunction is pointed up by their inclusion in a recently revised definition of PCOS, which was developed at a consensus meeting between The European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine. This new definition, which is so recent that it has not been applied in any studies discussed in this article, consists of the presence of polycystic ovaries and at least one of the two following criteria (a) oligo-ovulation/anovulation, or (b) clinical or biochemical evidence of hyperandrogenism (7).

Additional Endocrine Features of PCOS

Several metabolic abnormalities are characteristic of PCOS and are relevant to this discussion, particularly in light of antiepileptic drug (AED) side effects. Impaired glucose tolerance, as evidence of insulin resistance, is present in about 31% to 35% of women with PCOS and can occur in lean or obese women. In contrast, insulin resistance occurs in about 8% of the general population (8,9). Further, hyperinsulinemia resulting from insulin resistance perpetuates the development of PCOS. Insulin inhibits hepatic production of insulin-like growth factor binding protein-1 (IGFBP-1) and testosterone-binding globulin. The free fraction of both IGFBP-1 and testosterone, therefore, will be increased, but this is only part of the cascade of events. Insulin and IGFBP-1 both stimulate thecal androgen production;

therefore, the net effect of hyperinsulinemia is higher androgen production in the ovary as well as a greater bioactive fraction of androgen (10).

Another key hormonal feature of PCOS, relevant to discussion of PCOS in epilepsy, is elevated luteinizing hormone (LH) secretion from the pituitary and an increased ratio of LH to follicle-stimulating hormone (FSH). LH stimulates ovarian steroidogenesis, and elevated LH-to-FSH ratio will produce follicles that do not fully mature but, rather, become numerous and cystic. Immature follicles are deficient in aromatase, the enzyme that produces estrogen in the ovary by converting it from its precursor, testosterone. In this manner, the PCOS ovarian follicle manufactures primarily androgens. The abnormality is reinforced further by the conversion of androgen to estrogen by aromatase in the periphery, which results in elevated circulating estrogens that feed back to the pituitary and disrupt normal LH secretion (10).

PCOS and PCO in Epilepsy

Two recent studies involving large groups of women with epilepsy show that PCOS and ovulatory dysfunction occur at higher than expected rates in this patient population, with evidence of exacerbation of menstrual dysfunction associated with valproate use. In an evaluation of 93 women with focal epilepsy of long duration, PCOS (defined as elevated testosterone levels and oligomenorrhea or amenorrhea) occurred in 10.6% of patients. No difference was found among women taking carbamazepine ($n = 20$; 10%), valproate ($n = 18$; 11.1%), or no AEDs ($n = 19$; 10.5%) (11). The presence of PCOS was higher than that in the general population, however. Another study that evaluated menstrual dysfunction in 101 women with epilepsy seen consecutively in a clinic (36 patients' seizures were idiopathic generalized, and 65 were focal in onset) found inadequate luteal phase cycles (anovulatory) in 30% of the women, without a clear association with epilepsy type. However, valproate was associated with anovulatory cycles more frequently than were other AEDs (12). The expected frequency of anovulation in the general population would be about 8% to 10% (13); therefore, anovulation occurred much more frequently than expected in this population of women with epilepsy.

PCO have been found in a high percentage of women with epilepsy, as well. In a recent study of predictors of anovulation in women with epilepsy, PCO were found in 41% of 59 women with idiopathic generalized epilepsy (IGE), 26% of 35 women with localization-related epilepsy (LRE), and 16% of 23 healthy controls (13). The occurrence of PCOS in IGE significantly differed from that in controls in this study. Further, anovulation occurred in 27% of cycles in women with IGE, compared with only 14% with LRE and 11% of controls. The free testosterone levels were evaluated in association with specific AEDs within

each epilepsy type. These results again suggest an overall effect of epilepsy itself, because women with IGE taking valproate and women with LRE taking phenytoin or lamotrigine all had significantly higher free testosterone levels than did controls. The number of subjects who had testosterone levels outside the normal range is not reported; the mean levels were not abnormal for women. A significantly elevated LH/FSH ratio is another feature of PCOS and was present in the women with epilepsy in this study, compared with controls. The IGE group had the highest ratio, and 19 of the 35 women in this group used valproate.

Features of PCOS and PCO Associated with Valproate

In 1993, Isojarvi et al. (14) reported the first association between valproate and cystic ovaries. The authors stated that nearly half of the 28 women with epilepsy treated with valproate monotherapy had amenorrhea, oligomenorrhea, or prolonged menstrual cycles, compared with 19% of the 120 women taking carbamazepine monotherapy. For women taking valproate alone, or valproate plus carbamazepine, having menstrual disturbances was associated with elevated free testosterone. Forty-three percent of women receiving valproate alone had PCO, compared with 22% of women taking carbamazepine alone ($n = 120$), and 18% in normal controls ($n = 51$). This study does not clearly differentiate an effect of valproate from epilepsy itself on menstrual disturbances or elevated free testosterone. It is supportive of an association between valproate and cystic ovaries, however. In 1996, a second report from the same group demonstrated that 11 of 22 obese women with epilepsy, taking valproate, had insulin resistance and elevated androgen levels (15).

Another study evaluated hormone profiles in young men and women taking valproate ($n = 40$) or lamotrigine ($n = 36$) (16). Women, but not men, taking valproate ($n = 23$), on average, had significantly higher testosterone and free-androgen indices; however, only two women had testosterone levels outside the normal range. Insulin levels were higher in obese subjects overall. Menstrual cycle abnormalities occurred more frequently in women taking lamotrigine than valproate (7/21 vs. 5/23). A recent study by Morrell et al. (17) evaluated endocrine features of women with epilepsy who were administered lamotrigine monotherapy ($n = 119$) or valproate monotherapy ($n = 103$) for less than 5 years. With historical, not prospective, information, patients taking valproate were found to have gained more weight since starting the drug compared with those patients taking lamotrigine, although insulin levels were not significantly different. Additionally, no significant difference was found in menstrual cycle regularity or in anovulation between the two groups. Mean serum testosterone levels were higher in the valproate group compared with those in the lamotrigine group.

Another recent report of prepubertal and teenage girls with epilepsy ($n = 69$) found that androgen levels were higher in all subjects taking medication compared with girls with epilepsy not taking medication or with controls. Valproate was specifically associated with elevated androstenedione levels in every subject using it (18).

PCOS and PCO in Epilepsy: Valproate as a Confounder

As described, reports of women with epilepsy strongly point to an association between epilepsy and neurogonadal disease. Several series document the occurrence of the current diagnostic features of PCOS, which are ovulatory dysfunction and elevated androgens, more frequently than expected in women of reproductive age with epilepsy and irrespective of AED treatment. One specific feature necessary for the diagnosis of PCOS, which is elevated androgen levels, is associated particularly with valproate, however, and is reported consistently in many clinical series. These studies report an elevation in androgen levels for subjects taking valproate compared with that in subjects taking other AEDs or with controls; however, the actual levels of androgens with valproate are rarely outside the normal range for women.

Weight gain is a well-known side effect of valproate, but it is not a primary diagnostic feature of PCOS. Insulin resistance can be produced by weight gain itself; however, it is present as an independent endocrine dysfunction in both obese and lean women with PCOS. It is unknown whether valproate is associated with insulin resistance in patients who do not gain weight while taking the drug. Menstrual dysfunction and anovulation have been reported more frequently in women with epilepsy, but the association with valproate in epilepsy is mixed. PCO seem to be overrepresented in women with epilepsy and, in some reports, are specifically associated with valproate. The clinical significance of this fact as an independent finding is unclear, but it is likely that it is, at the least, a harbinger of anovulation and subfertility.

Mechanisms Underlying the Occurrence of PCOS in Epilepsy

The most plausible theory as to how epilepsy can cause PCOS, or at least a reasonable facsimile of it, concerns the mechanism of elevated LH, as described previously in this article. Investigators speculate that epilepsy, a disease of the brain, affects the brain in such a manner that it secondarily influences the reproductive system, for example, affecting the hypothalamic–pituitary axis (HPA). This hypothesis was first proposed by Herzog et al. in 1986 (19) and has been studied very little since then—although a study paradigm that evaluates the effects of seizures and epilepsy on the hypothalamus is not simple

to envision. The sequence of events leading to elevated LH secretion begins as follows: seizure discharges, either ictal or interictal and involving medial temporal areas, stimulate the secretion of gonadotropin-releasing hormone (GnRH). Next, increased GnRH pulse frequency promotes the secretion of LH at a greater levels than the secretion of FSH and results in an elevated LH/FSH ratio (20).

Herzog et al. (21) studied LH pulse frequencies in women with epilepsy and found that the pulse frequency is increased, with an especially marked increase in left temporal lobe epilepsy. Furthermore, evidence for reproductive dysfunction in epilepsy based on a mechanism of HPA dysfunction has been reported. Earlier-than-expected menopause has been described in women with high seizure rates—a finding that likely is also a manifestation of subtle HPA dysfunction, leading to early ovarian failure (23). Therefore, the reproductive abnormalities in women with epilepsy of reproductive age, that is, ovulatory dysfunction and elevated circulating androgens, which either look like or actually are PCOS, could be the result of seizures or interictal discharges affecting the HPA.

Mechanisms by Which Valproate Causes Elevated Androgens and PCO

Valproate induces androgen synthesis in the ovary, likely as a result of multiple mechanisms. One study using human ovarian thecal cell cultures showed that valproate induced ovarian androgen synthesis by augmenting transcription of steroidogenic genes (24). Another report used ovarian follicles in culture with ovarian thecal and granulosa cells, so as to replicate an ovary, and showed that valproate increased testosterone secretion from follicles but had differing effects based on the degree of LH stimulation in the culture and on maturity of the follicles (25). Further, valproate decreased the conversion of testosterone to estradiol, suggesting an inhibitory effect on the converting enzyme, aromatase (25). This finding is interesting in light of the recent exploration of aromatase inhibition as a possible treatment for epilepsy, which is based on the theory that decreased brain estrogen in men will promote a seizure-inhibiting hormonal milieu (26).

Valproate produced ovarian cysts in nonepileptic Wistar rats at very high, suprathreshold doses (27). A study more applicable to humans, however, evaluated the effects of valproate on nonepileptic, normally cycling female Rhesus monkeys, who were treated for 12 to 15 months and, compared with control monkeys, achieved therapeutic levels of valproate similar to those in seen in humans (28). No effects on menstrual cycling (which normally is nearly identical to that in humans), ovulation, androgen levels, LH/FSH ratio, insulin response, or lipid profiles were found. The ovaries, on pathologic evaluation, were normal as well. These results suggest that the effects of valproate

in women with epilepsy could be due to valproate exacerbating an already disturbed system, which is unable to compensate for its androgen-promoting actions.

Conclusions

PCOS has multiple etiologies; none is fully understood (10). Its occurrence is under genetic influence as well as related to ovarian, hypothalamic, and glucose-modulating dysfunction. In this light, it is difficult to state what exactly is the reproductive dysfunction related to epilepsy. Is it PCOS, or is it a neurologic or epileptic variant? Further, valproate can produce at least one symptom (increased androgens) and one sign (obesity) present in PCOS; yet the question remains whether it causes PCOS or a valproate-related variant of PCOS. It also is possible that neuropsychiatric illness is a prerequisite for the clinical expression of endocrinopathy related to valproate (10). Certainly, the use of valproate in epilepsy confounds the sorting out of independent associations with PCOS.

This review is not comprehensive; other more thorough reviews have been published (10,29–32). It seems prudent that clinicians educate themselves on the prevalence of PCOS in epilepsy before recommending the use of valproate, or any AED, to female patients and then continue to monitor female patients from adolescence to menopause, looking vigilantly for signs of POCS. POCS is associated with many health risks including type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial cancer (10). More information is needed about the use of valproate in women with epilepsy and its risk of inducing PCOS. Common sense would dictate that, for a woman with epilepsy who has evidence of PCOS, the use of valproate should be judiciously considered.

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