

# Polycystic ovarian syndrome in epileptic Kashmiri women on sodium valproate and phenytoin: A case control study

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## Abstract

**Background & Objectives:** Polycystic ovarian syndrome (PCOS) is a common cause of infertility in women of reproductive age group. Antiepileptic drugs, notably sodium valproate, has been linked to PCOS in various studies. Such an association has significant implications given rampant use of sodium valproate, particularly in such women. The purpose of the study was to compare the incidence of PCOS in women taking valproate or phenytoin monotherapy with healthy controls. **Methods:** Thirty five women on valproate monotherapy and 28 women on phenytoin were compared with 43 healthy women. **Results:** Mean BMI was 24.46 kg/m<sup>2</sup> (SD 4.19) in valproate group, 23.37 kg/m<sup>2</sup> (SD 3.67) in phenytoin group and 22.12 kg/m<sup>2</sup> (SD 3.29) in control group. Menstrual dysfunction was seen in 40% patients in valproate group which was significant as compared to phenytoin group (14%) and control group (12%). Polycystic ovaries were seen on ultrasonography in 37% patients in valproate group, 18% in phenytoin group and 14% in control group. Serum testosterone, prolactin, LH and LH/FSH ratio were significantly higher in valproate group as compared to Control group (p value < 0.05). Twenty six percent patients in valproate group had PCOD while as 14% in the Phenytoin group and 7% in Control group were diagnosed as PCOD.

**Conclusion:** Women with epilepsy taking sodium valproate for seizure control have higher prevalence of menstrual dysfunction and PCOS and hence need closer follow up and health advice.

**Keywords:** PCOS, valproate, phenytoin, epilepsy, seizure.

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common cause of menstrual irregularities and infertility in women. First described by Stein and Leventhal in 1935 as a phenotype of amenorrhea, hirsutism, obesity and characteristic polycystic ovaries, PCOS is today known as a well-recognized syndrome in women of child bearing age with major cardiovascular, metabolic and reproductive dimensions.<sup>1</sup> Presently PCOS is viewed as a state of clinical and/or biochemical hyperandrogenism with or without chronic anovulation in the absence of specific adrenal or pituitary disease.<sup>2</sup> Based on the different diagnostic criteria used for the diagnosis of PCOS, the prevalence of this disease varies from 6 to 18%.<sup>3-5</sup> This variation is also accounted by different ethnicity of the studied populations and different socioeconomic

and geographical factors. Etiology of PCOS is complex and is intimately linked with insulin resistance and hyperinsulinemia. Most women with PCOS have a hyper-insulinemic response to a glucose challenge and around 7-10% have overt type 2 diabetes mellitus in addition to 30% PCOS women who have impaired glucose tolerance.<sup>6-9</sup>

The relationship of epilepsy with PCOS is complex. Several antiepileptic drugs (AEDs) are associated with increased incidence of PCOS through several mechanisms including altering the levels of reproductive hormones in the human body thus causing reproductive dysfunction.<sup>10,11</sup> Besides it has been proposed that abnormal electrical discharges in epilepsy affect several endocrine glands thus further altering the hormonal milieu. PCOS is particularly associated with temporal lobe epilepsy.<sup>12-14</sup> There is a paucity

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of data regarding PCOS in Asian women with epilepsy, particularly in Indian subcontinent. The present study was done to investigate the prevalence of PCOS in Indian women with epilepsy in a north Indian tertiary care hospital.

The aim of this study was to compare the incidence of PCOS in women with epilepsy on sodium valproate or phenytoin monotherapy with healthy controls.

## METHODS

Sixty three women with epilepsy fulfilling the inclusion/exclusion criteria, in the reproductive age group (13 - 45 years) were included in the study. Thirty five women were on valproate monotherapy and twenty eight women were receiving phenytoin for seizure control. Forty three healthy women in the reproductive age group served as controls.

The inclusion criteria were: Females between 13-45 years of age; diagnosed case of epilepsy; and patients on sodium valproate or phenytoin monotherapy for at least six months. The exclusion criteria were: Patients who did not consent; pregnancy/lactation; patients on antiepileptic polytherapy; use of exogenous steroids and drugs causing ovarian failure; and presence of Cushing's syndrome, acromegaly, congenital adrenal hyperplasia or androgen secreting tumors.

### *Clinical evaluation*

Complete history including duration of seizures, type and dose of AED, and types of menstrual disturbances was obtained. Menstrual disturbances were defined as amenorrhea (absence of menstruation for 6 months), oligomenorrhea (interval between episodes of menstruation greater than 35 days), menorrhagia (bleeding that lasts more than 7 days a cycle) or polymenorrhea (interval between episodes of menstruation less than 21 days).

Age, weight, height, body mass index (BMI) and waist-hip ratio(WHR) of patients were recorded and signs of hyperandrogenism were checked. Clinical hyperandrogenism was defined as presence of acne/hirsutism/androgenic alopecia. Hirsutism was scored as per the modified Ferriman - Gallway Score and a score of more than eight was considered significant for a diagnosis of hirsutism.

Venous blood samples were drawn in the early follicular phase (day 3-5) of the menstrual cycle for the analysis of serum testosterone,

luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and thyroid stimulating hormone (TSH), lipid profile and fasting blood glucose. Serum hormonal analysis was done by chemiluminescence assays. Biochemical hyperandrogenism was defined as serum total testosterone values 86 ng/dL or more.

A transabdominal ultrasound was performed using a 2 -5 MHz transducer to look for ovarian diameter, number and mean size of ovarian follicles and stromal echogenicity.

### *Diagnosis of polycystic ovarian syndrome*

The diagnosis of polycystic ovarian syndrome was based on the Rotterdam criteria as follows: Oligomenorrhea (less than 6-9 menses per year) and/or anovulation; clinical and/or biochemical hyperandrogenism (elevated total/free testosterone); polycystic ovaries on USG ( $\geq 12$  antral follicles measuring 2-9 mm in diameter in one ovary or ovarian volume  $\geq 10$ cc in at least one of the ovaries) and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome).

### *Statistical analysis*

A student's t test and Fischer exact test were performed for comparison between the different groups. The level of significance was established at p value less than 0.05. Data are represented as the mean  $\pm$  SD.

## RESULTS

The mean age of patients receiving sodium valproate was 23.02 years (SD 3.48), while as those receiving phenytoin sodium was 21.71 years (SD 2.81). Mean age of women in control group was 23.27 (SD 3.64) and the difference in age in all three groups was statistically insignificant (p value 0.14). The mean fasting blood sugar (mg/dl) was higher in valproate group ( $93.42 \pm 10.13$ ) as compared to phenytoin ( $88.07 \pm 9.03$ ) and control group ( $87.55 \pm 8.49$ ). The difference was significant only in valproate group vs control group (p value  $< 0.05$ ). Similarly dyslipidemia was more common in valproate group (Table 1).

Mean BMI was 24.46 kg/m<sup>2</sup> (SD 4.19) in valproate group, 23.37 kg/m<sup>2</sup> (SD 3.67) in phenytoin group and 22.12 kg/m<sup>2</sup> (SD 3.29) in control group. Compared to control group, both valproate and phenytoin group had higher mean BMI which was statistically significant. However difference in mean BMI in phenytoin and valproate

**Table 1: Lipid profile in different patient groups**

Variable (mg/dl)	Valproate	Phenytoin	Control
Total cholesterol	180.25±53.52	165.07±62.90	154.16±42.41
HDL	40.65±11.05	43.5±9.72	48.53±8.27
LDL	93.54±24.89	81.5±28.57	76.90±28.89
Triglycerides	230.31±89.03	202.39±96.04	146.65±82.5

group was not significant. As shown in Figure 1, 45% patients in valproate group had BMI  $\geq 25$ kg/m<sup>2</sup> while as 28% patients in phenytoin group were overweight. The difference was however statistically insignificant (p value 0.19). Mean waist-hip ratio (WHR) was  $0.830 \pm 0.056$  in Valproate group which was slightly higher than in the phenytoin group ( $0.820 \pm 0.041$ ). Both these groups had higher WHR as compared to control group ( $0.804 \pm 0.045$ ) although the difference was statistically significant only with the valproate group.

Menstrual dysfunction was seen in 40% patients in valproate group which was significant as compared to Phenytoin group (14%) and control group (12%). Similarly more number of patients had hirsutism in valproate group (20%) as compared to phenytoin (12%) and control group although statistically the difference was not significant. Similarly acne was more common in valproate group (40%) as compared to phenytoin (36%) and control groups (23%) although differences were not significant amongst groups. Alopecia also was higher in valproate group (20%) compared to phenytoin (18%) and control group (9%), The differences did not reach statistical significance.

Polycystic ovaries were seen on ultrasonography

in 37% patients in valproate group which was higher as compared to phenytoin group (18%) and control group (14%). The difference reached statistical significance only in valproate vs control group.

Serum testosterone, prolactin, LH and LH/FSH ratio were significantly higher in valproate group as compared to control group (p value < 0.05). These were also elevated in phenytoin group compared to control group but difference was significant only in serum prolactin. Similarly all these hormones were higher in valproate group compared to phenytoin group but differences were not statistically significant (Figure 2).

Twenty six percent of patients in valproate group fulfilled the criteria required for the diagnosis of PCOD while as 14% in the phenytoin group and 7% in control group were diagnosed as PCOD. Compared to control group the difference was significant in valproate group (p value 0.029) and insignificant in phenytoin group (p value 0.42). (Figure 3).

## DISCUSSION

Valproate is an antiepileptic drug used to treat epilepsy, migraine and bipolar disorders. Its unfavorable side effect includes weight gain

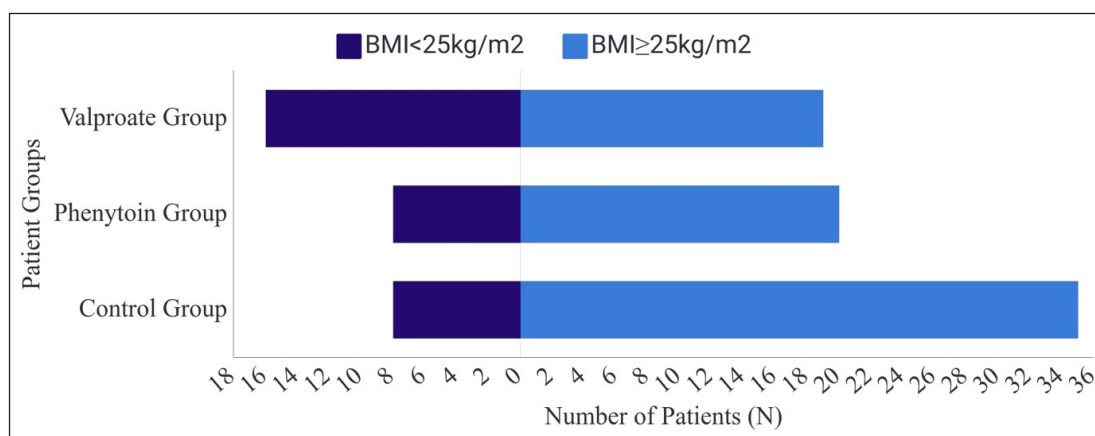


Figure 1. Number of overweight patients in each group.

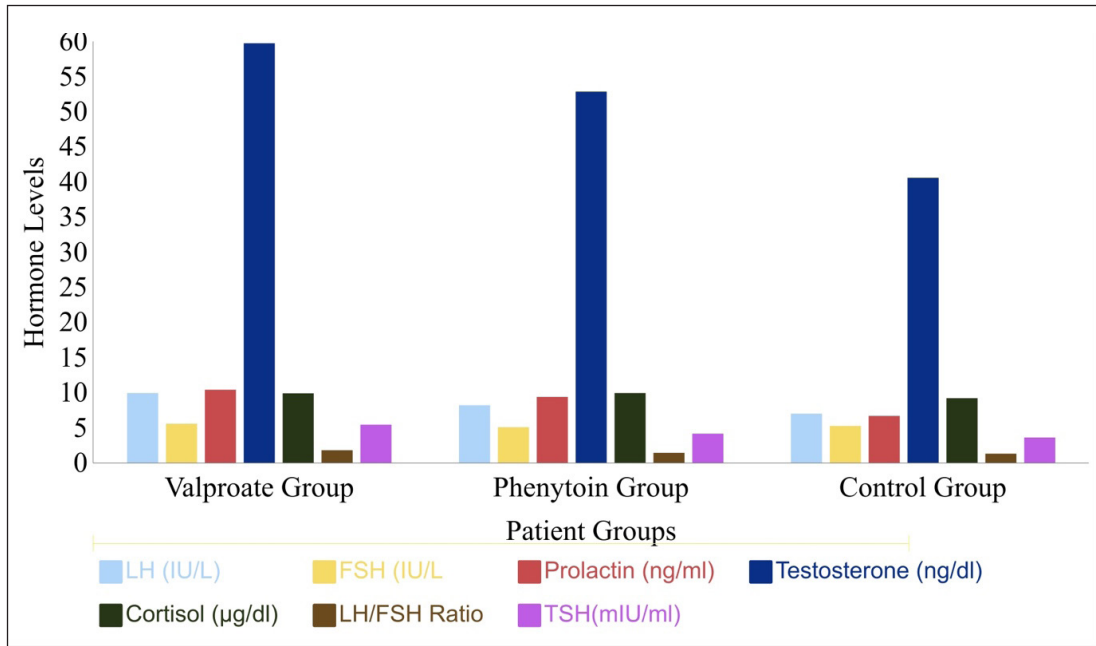


Figure 2. Hormonal profile of different patient groups and control group.

occurring in around 58% patients, more so in women.<sup>15</sup> An average of 6 kg is gained on valproate therapy.<sup>16</sup> In our study, weight of women in valproate group was higher as compared to women in phenytoin and control groups signified by higher BMIs. The exact mechanisms responsible for weight gain with valproate are not fully understood. Increased hunger, binge eating, fast

food cravings and depression are some of the mechanisms that have been put forward as possible mechanisms.<sup>17</sup> Phenytoin has not been associated with weight gain.<sup>18</sup> Although the distribution of fat gain in patients on valproate therapy is global, abdominal fat increases by 7% more than that total body fat by percentage resulting in increase in waist-hip ratio.<sup>19</sup> As seen in our

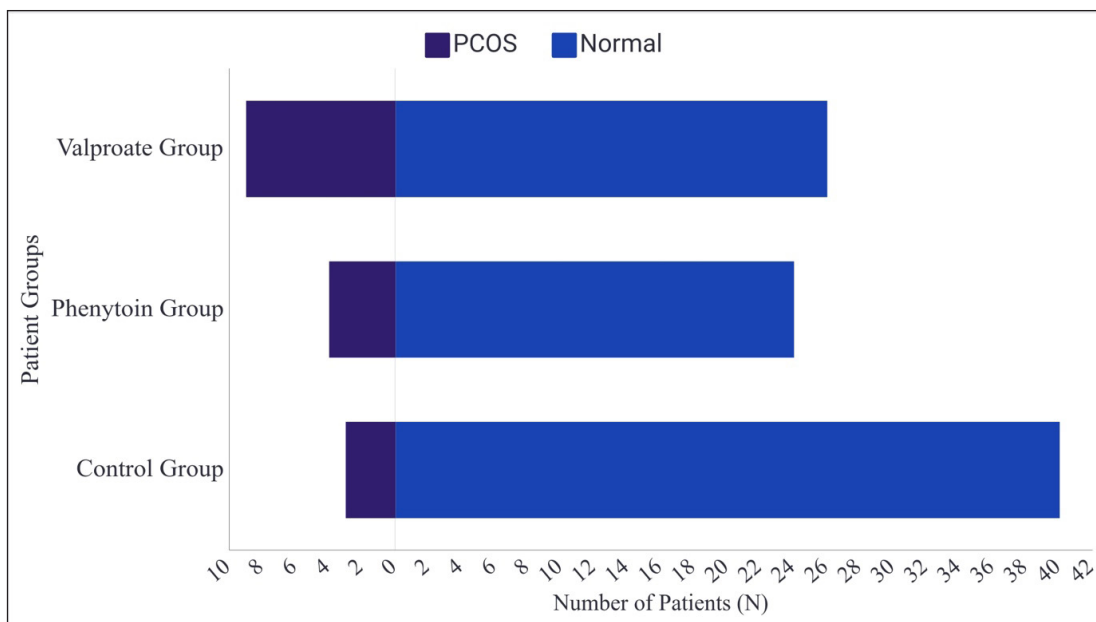


Figure 3. Number of PCOD patients in each group.

study, the WHR in valproate group is higher as compared to phenytoin and control group. Besides, Valproate group had higher fasting glucose and lipid levels and as such warrants evaluation for metabolic syndrome in these patients. Clinically metabolic syndrome comprises at least three of the following: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated fasting glucose and is a marker of atherosclerotic cardiovascular and peripheral artery disease. Phenytoin has been shown to increase levels of LDL, LP(a) and TGs although not as much as valproate. The studies on effect of valproate on blood sugar level have given conflicting results. Initially thought to cause insulin resistance scientists now believe it causes increased secretion of insulin as well as decreases its degradation resulting in higher insulin levels without insulin resistance.<sup>20</sup> The effects of such metabolic arrangement could be lower fasting blood sugars as shown in several studies in rats and humans. Such an effect would also mean its use in management of diabetes in future if studies support this effect.

Most of the patients on sodium valproate develop abnormal pituitary hormonal milieu. Serum levels of testosterone (free and total), LH and prolactin are usually high.<sup>21</sup> Valproate induced hyperandrogenemia may be due to inhibition of conversion of testosterone to estradiol by aromatase or due to inappropriate LH surges.<sup>22</sup> The resulting action may be a part of its antiepileptic effect as dehydroepiandrosterone sulfate, a metabolite of testosterone, has anticonvulsant properties while as estradiol is a proconvulsant. Valproate has different effect on pituitary hormonal status in men and women. Women on sodium valproate therapy have higher levels of gonadotrophins particularly LH that could either be a primary phenomenon or a feedback effect secondary to PCOS. However the rise occurs early in the course of sodium valproate treatment, hence supporting the former view.<sup>23</sup> Women on valproate, in our study, had significantly higher LH, LH/FSH and prolactin levels compared to control group. Men on valproate therapy have been found to have lower levels of serum testosterone, LH, FSH and higher levels of prolactin. This may result in lower sperm counts and higher infertility rates in men on valproate therapy.<sup>24</sup>

Reproductive endocrine disorders like PCOS, menstrual dysfunction occur frequently in women taking antiepileptic drugs particularly sodium valproate. Initial reports of a possible

association between valproate therapy and menstrual abnormalities came from several case reports of women with epilepsy using valproate, in whom these menstrual irregularities disappeared after discontinuation of the drug.<sup>25,26</sup> The risk of developing PCOS during valproate treatment seems to be higher in women with epilepsy than in women with bipolar disorders.<sup>27</sup> The exact mechanism of valproate causing PCOS has not been entirely elucidated. Amongst the many theories, the one put forward by Woods *et al.* looks more reasonable.<sup>28</sup> They compared the gene expression profiles of untreated normal, Valproate-treated normal, and untreated PCOS theca cells and demonstrated similarities in the gene expression profiles of valproate-treated normal and PCOS theca cells. Their experiments show that valproate alters global gene expression in the human theca cell such that it exhibits a PCOS-like molecular phenotype.

Similar metabolic and reproductive side effects of sodium valproate have been documented in Indian women on long term valproate therapy, although results from different studies have been conflicting. In one of the studies, clinically relevant weight gain was found in 40% women on valproate therapy while as menstrual irregularities were seen 24% patients.<sup>29</sup> PCOS was diagnosed in 20% patients in this study. In another study, although patients on sodium valproate had higher prevalence of PCOS compared to normal population, the difference between epileptic women on valproate compared to untreated epileptic women was not significant.<sup>30</sup> Qadri *et al.* reported the prevalence of PCOS in 19.3% Kashmiri women taking sodium valproate for bipolar disorder.<sup>31</sup> In our study, mean BMI and obesity were significantly higher in Valproate group compared to controls. Besides the prevalence of menstrual dysfunction and PCOS was 40% and 26% respectively in the valproate group, significantly much higher than in control group. Also the prevalence of PCOS in our studied population on valproate was higher than reported by Qadri *et al.* The difference could be due to the different set of populations studied, as our patients had epilepsy while as theirs had bipolar disorder.

In conclusion, sodium valproate is a commonly used drug in different neuropsychiatric diseases worldwide. It has been consistently found to be associated with metabolic and reproductive side effects including PCOS that may have a bearing on fertility and cardiovascular risk factors in women of reproductive age group. Reasonable



screening protocols for PCOS and general advice on reducing cardiovascular risk factors in such women should be promoted. Wherever feasible, alternative epileptic drugs can be used to maintain seizure control in such women.

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