Original Article

Polycystic Ovary Syndrome in Bipolar Affective Disorder: A Hospital-based Study

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ABSTRACT

Background: Preliminary studies suggest a multidimensional relationship of mood pathology with endocrine disturbances. Studies have found an increased risk of mood disorders in polycystic ovary syndrome (PCOS), and conversely, many of the medications commonly used in the treatment of bipolar affective disorder (BPAD) can have deleterious effects on blood levels of reproductive hormones and consequently on the hypothalamic–pituitary–gonadal (HPG) axis and reproductive function. Furthermore, there is evidence of reproductive dysfunction in women with BPAD before treatment. **Objectives:** To assess the comorbidity of PCOS in patients of BPAD and to study risk factors associated with this comorbidity. **Materials and Methods:** Two hundred female patients with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition diagnosis of BPAD, between ages of 15 and 45 years, were evaluated by an endocrinologist. Patients reporting menstrual disturbances or having any stigmata of PCOS were further subjected to hormonal analysis, which included luteinizing hormone, follicle-stimulating hormone, prolactin, and testosterone, in the early follicular phase of menstrual cycle. Diagnosis of PCOS was made as per the NIH criteria. **Results:** Of 200 patients, 46 (23%) were diagnosed as having PCOS. Forty-five percent ($n = 90$) reported menstrual disturbances while 27% ($n = 54$) had polycystic ovaries on ultrasonography. 19.2% of the patients diagnosed as PCOS had a history of valproate intake while 27.90% patients had no such history ($P = 0.15$). No significant difference ($P = 0.07$) was found in the prevalence of PCOS among various drug groups (including group on multiple mood stabilizers). **Conclusion:** A higher prevalence of PCOS is seen in BPAD, irrespective of pharmacotherapy, suggesting a common link between the disorders which might be in the form of disturbance in HPG axis.

Key words: *Bipolar affective disorder, mood disorders, polycystic ovary syndrome, psychiatric comorbidities*

INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the most common endocrine disorder of women,[1] is a heterogeneous disorder of unclear etiology, most simply defined as the presence of hyperandrogenism (clinically and/or biochemically) and/or chronic anovulation in the absence of specific adrenal and/or pituitary disease.[2] This syndrome was first described by

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Stein and Leventhal in 1935[3] although the presence of sclerocystic ovaries had been recognized for at least 90 years before their report. Numerous theories have been put forward since then; however, the current perspective is that PCOS is a complex genetic trait, similar to cardiovascular disease, Type 2 diabetes mellitus, and metabolic syndrome, where multiple genetic variants and environmental factors interact to foster the development of the disorder.

Polycystic ovary syndrome and psychiatric disorders

Studies have shown a high prevalence of mood and anxiety disorders in patients with PCOS. Women with PCOS have higher depression scores and a higher risk of depression independent of body mass index (BMI). These data underscore the need to screen all women with PCOS for mood and anxiety disorders and adequately treat women who are diagnosed with these conditions.

Polycystic ovary syndrome and bipolar affective disorder

A connection between PCOS and bipolar affective disorder (BPAD) was suggested by Matsunaga and Sarai[4] and further clarified by Rasgon *et al*.[5,6] In these studies, the authors suggested that a relationship might exist between abnormal menstrual cycles and bipolar symptoms, resulting in a higher prevalence of PCOS in women with BPAD. Theories have been formulated to explain the high prevalence of PCOS in these populations which include the effects of antimanic agents, such as valproate. This connection was first presented in a 1993 article by Isojärvi *et al*.,[7] which found ultrasound evidence of polycystic ovaries (PCOs) in 43% of epileptic outpatients taking valproate. Along with a later publication by Isojärvi *et al*.,[8] the conclusion was that PCOS may be positively associated with valproate use. Similarly, a study by O'Donovan *et al*.[9] found that 47% of female bipolar patients taking valproate had menstrual abnormalities, compared to 13% of those patients not taking valproate.

Similar metabolic disorders are associated with both PCOS and BPAD, such as insulin resistance (IR), obesity, hyperleptinemia, and hyperactivation of the hypothalamus–pituitary–adrenal (HPA) axis. These common morbidities may represent an indirect link between PCOS and BPAD. For instance, one paper supports the hypothesis that PCOS is stimulated by decreased peripheral insulin sensitivity and hyperinsulinemia,[10] while another review suggests that glucocorticoid resistance results in impaired negative feedback mechanisms, HPA hyperactivity, and overproduction of mineralocorticoids and androgens in PCOS.[11] Likewise, IR, disturbances in HPA, and hypersecretion of cortisol have been documented in both depressive and manic phases of BPAD.[12,13] These similarities between the diseases and the predisposition for common symptoms suggest possible pathophysiological overlap.

Thus, PCOS and BPAD are complex, polygenetic disorders that share common endophenotypes in IR, hyperlipidemia, and other metabolic abnormalities. The incidence of PCOS is also higher in bipolar patients and vice versa. Further research is necessary to crystallize the common genetic associations between the two disorders. Linkage studies could focus on chromosomal loci overlap between the two disorders to identify candidate genes related to metabolism.[14]

The goal of our study was to assess the comorbidity of PCOS in bipolar patients. We have also tried to find out the effects of mood stabilizers, antipsychotics, and other psychotropics on the rates of PCOS as previous studies have shown increased rates of PCOS with the use of valproate (a commonly used mood stabilizer).

Very scarce literature is available on association between BPAD and PCOS, and in fact, our search in PubMed, MEDLINE, and Google Scholar, using keywords: polycystic ovary syndrome and bipolar affective disorder, psychiatric comorbidities, mood disorders, did not reveal any study from Asia, hence the importance of studying such an association in our population.

Objective

The aim of our study was to find out the proportion of PCOS in patients of BPAD and to study risk factors associated with this comorbidity.

MATERIALS AND METHODS

This was an observational descriptive type of study conducted at the Institute of Mental Health and Neurosciences, Kashmir (Government Psychiatric Diseases Hospital, Srinagar); an associated hospital of Government Medical College, Srinagar; the only hospital for mental health in the whole of Kashmir and the main referral institution for all patients suffering from any psychiatric disease or condition from all over the state. The research work was initiated following approval by the Board of Research Studies of Government Medical College, Srinagar. All ethical considerations were taken care of during the study.

Patient selection

Two hundred consecutive female patients fulfilling the inclusion and exclusion criteria in the age group of 15–45 years attending our outpatient department (OPD) were taken up for the study. The sample size was calculated using the Sample

size determination in health studies: A practical manual (WHO Geneva 1991),[15] presuming a prevalence of 50% as true prevalence is not known.

Inclusion criteria

- Females 15–45 years of age
- Diagnosis of BPAD.

Exclusion criteria

- Who did not consent
- Pregnancy (current or within the last 6 months)
- Use of exogenous steroids and drugs causing ovarian failure
- Presence of adrenal and pituitary disorders
- Patients with diabetes mellitus.

Methods

Two hundred consecutive patients attending our OPD and diagnosed as BPAD by consultant the psychiatrist according to criterion given in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), Text Revision,[16] fulfilling the inclusion and exclusion criteria, were enrolled for the study. Written informed consent was obtained from each patient in the local language understandable to the patient; those who were considered incapable of consenting participated in the study with the consent of their closest family member or custodian.

A detailed history was taken from the patients. Relevant data in the history, apart from sociodemographic profile, included age of onset of BPAD, duration of illness, duration of treatment, course of illness (number of mood episodes), history of valproate intake anytime during the illness and its duration, current drug history, family history, and menstrual history. Menstrual history included age of menarche, regularity, duration of cycles, and number of cycles per year or intermenstrual interval. Oligomenorrhea was defined as intermenstrual interval of ≥35 days or a total of ≤8 menses per year. Amenorrhea was defined as the absence of menstruation for the last 6 or more months. Polymenorrhea was defined as intermenstrual interval of ≤21 days.

The physical examination, apart from a general review of the systems, focused on the assessment of androgen status (hirsutism, temporal recession of hair, acne), evidence of IR (acanthosis nigricans), and anthropometry, (BMI, waist-to-hip ratio [WHR]). Body weight and body height were measured while standing with light clothing and no shoes. BMI was calculated as weight (kg) divided by height (m) squared. Waist circumference was measured in centimeters at the midpoint between the iliac crest and lower rib margin at the end of expiration. Hip circumference was measured in centimeters at the widest point between waist and thighs. WHR was calculated as the ratio of waist and hip circumferences. Quantification of hirsutism was done using modified Ferriman–Gallwey score[17] by counting of nine body areas by a single observer. A score of ≥8 of 36 was taken as statistically significant.

All patients were assessed by an endocrinologist. Patients reporting menstrual disturbances or having any stigmata of PCOS were further subjected to hormonal analysis, which included luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and testosterone. The fasting blood sample was taken in the early follicular phase (2nd day of menstrual cycle) of spontaneous or medroxyprogesterone-induced cycle for hormonal profile. Pooled samples of LH, FSH, prolactin, and total testosterone were estimated by chemiluminescent immunoassay. In addition, routine investigations, wherever deemed necessary, were carried out. Transabdominal ultrasound was performed using a 5 MHz transducer (HDI-5000 Philips MATRIX IU22, Bothell, WA, USA) to rule out other causes of hyperandrogenism.

Diagnosis of PCOS was made as per the NIH criteria by the endocrinologist.

Statistical testing was conducted with the Statistical Package for the Social Science system version IBM® SPSS® Statistics 20. Continuous variables are presented as mean ± standard deviation and are categorized into groups, and categorical variables are presented as frequencies and percentage. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. The comparison of normally distributed continuous variables between the groups was performed using Student's *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

This study included 200 female patients of BPAD in the reproductive age group. The mean age of our study population was 24.96 ± 6.6 years, with a minimum age of 15 years and a maximum of 42 years. All patients were seen in remission phase. Of 200 patients, 114 (57%) had a history of divalproex sodium intake. Mean dose of divalproex sodium was 1087.5 mg per day while mean duration of divalproex intake was 20.86 ± 19.18 months with maximum duration of 5 years (60 months) and minimum duration of 15 days. 29.5% (n = 59) were taking divalproex sodium as mood stabilizer at the time of assessment, 24%(n = 48) were taking lamotrigine, 5% (n = 10) were taking other mood stabilizers (such as carbamazepine, levetiracetam, lithium), 30% (n = 60) were only on antipsychotics, and 11.5% (n = 23) were

on multiple mood stabilizers in different combinations (e.g., divalproex sodium and lithium, lamotrigine, and lithium). Twenty-eight percent (n = 56) of our patients had oligomenorrhea, 16% (n = 32) had polymenorrhea, and 1% (n = 2) had secondary amenorrhea. Twenty-four percent (n = 48) had bilateral PCO while 3% (n = 6) had unilateral PCO on ultrasonography.

Of total 200 patients studied, 46 patients were diagnosed as having PCOS by endocrinologist, using the NIH criteria. Thus, the overall prevalence of PCOS in our sample was 23%. The mean age of patients with PCOS was 22.21 ± 5.06 years, while the mean age of those with no PCOS was 25.77 ± 6.80 years. Using Student's t-test, the difference was statistically significant (P = 0.0002). The prevalence of PCOS was 18.32% (24/131) in the rural population, while it was 31.88% (22/69) in urban population. Using Pearson Chi-square test, the difference was statistically significant (P = 0.03).

The prevalence of PCOS was 27.9% among patients who had no history of divalproex sodium intake anytime during their illness, while it was 19.3% among patients who had taken divalproex sodium. The difference was statistically not significant (P = 0.15).

Of 200 patients, 30% (n = 60) of the patients were on antipsychotics (mostly second-generation antipsychotics), and of these, 23.3% (n = 14) had PCOS. 29.5% (n = 59) were on divalproex sodium, of which 20.3% (n = 12) had PCOS. 24% (n = 48) were on lamotrigine, of which 20.8% had PCOS. 11.5% (n = 23) were on multiple mood stabilizers, of which 17.4% had PCOS. 5% (n = 10) were on other mood stabilizers such as carbamazepine, lithium, and levetiracetam, of these 60% (n = 6) had PCOS.

DISCUSSION

BPAD is a chronic remitting and relapsing illness that causes significant burden to patients, families, and society. It has been identified as the sixth leading cause of disability-adjusted life years worldwide among people between 15 and 44 years of age by the World Health Organization.[18] Although the pyknic somatotype was theorized as early as 1931 by Kretschmer, the exploration of neuroendocrine aspects of BPAD has begun recently. The concern initially arose from a study conducted by Isojärvi *et al*. that found menstrual disturbances in epileptic outpatients taking valproate, a commonly used mood stabilizer.[7] This data set sparked debate and a series of studies evolved which suggested a two-tiered relationship of mood pathology with endocrine disturbances. First, many of the medications commonly used in the treatment of BPAD can have deleterious effects on blood levels of reproductive hormones and consequently on the HPG axis and reproductive function. Second, there is evidence of reproductive dysfunction in women with BPAD before treatment.[19] Further, it has been hypothesized that PCOS and BPAD are complex, polygenetic disorders that share common endophenotypes in IR, hyperlipidemia, and other metabolic abnormalities.[14]

Owing to lack of any substantial data concerning the relationship of PCOS and BPAD, the current study was designed to explore this issue by screening for PCOS in a population of women diagnosed with BPAD. We further sought to identify various factors which can put the women with bipolar illness at risk of getting PCOS.

Using the NIH criteria, 23% of our study population was diagnosed as having PCOS, which is much more than the estimated prevalence of 4%–8% in studies performed in Greece, Spain, and the USA using the same criteria.[2,20,21] Due to the logistics of diagnosis and lack of consensus on the diagnostic criteria, there are very few prevalence studies in the community, especially from India. Gill *et al*.[22] found a prevalence of 3.7% in college girls (18–24 years) from Lucknow, North India, while Nidhi *et al*.[23] reported a prevalence of 9.13% in adolescents (15–18 years) from Andhra Pradesh, South India. Former used NIH criteria while latter used Rotterdam criteria for the diagnosis of PCOS which might explain the difference in results. In a recent study comparing various diagnostic criteria, it was found that the Rotterdam and Androgen Excess Society prevalence estimates were up to twice than that obtained with the NIH criteria.[24] In a recent questionnaire-based survey in our valley, 33% were identified as probable PCOS and 3.1% were known cases of PCOS. However, the study is still in its initial phase and definitive conclusions cannot be drawn as of now (Ganaie, unpublished data).

Although there are no published community studies from our state, PCOS has been studied in various specific groups. In one such study by Zargar *et al*., the prevalence of PCO and PCOS was estimated in women with Type 2 diabetes mellitus and nondiabetic control women and it was found that PCOS was present in 37.1% of diabetic subjects and 25% of nondiabetic controls, suggesting a higher prevalence of PCOS in our community.[25] Rotterdam criteria were used for diagnosis of PCOS in this study which might, in part, explain such results. Comparing our results with the control group of this study, no significant difference can be seen (23% vs. 25%). This is in accordance with the observations made by Rasgon *et al*., who found a prevalence of 5.5% in 72 females with bipolar disorder, a proportion similar to their population rates.[5]

A connection between PCOS and BPAD was suggested by Matsunaga and Sarai and further clarified by Rasgon *et al*.[4,5] In these studies, the authors suggested that a relationship might exist between abnormal menstrual cycles and bipolar symptoms, resulting in a higher prevalence of PCOS in women with bipolar disorder. Based on the findings by Isojärvi *et al*.,[7] most of the earlier research focused on the role of drugs, especially valproate, in causing PCOS. In one such study by O'Donovan *et al*., seven of the 17 women receiving valproate had menstrual abnormalities and five of these seven had high free and total testosterone levels consistent with PCOS.[9] Thus, 5/17 or 29% of the sample receiving valproate appeared to have laboratory and menstrual findings suggestive of PCOS. However, no hormonal assays were obtained from women with menstrual abnormalities who were not taking valproate to assess the rate of hypertestosteronemia. Similarly, data from the Systematic Treatment Enhancement Program for Bipolar Disorder on the prevalence of PCOS in women with bipolar disorder receiving mood stabilizers also suggest that valproate use in adult women may carry an elevated risk of PCOS, as nine out of 86 women, or 10.5%, taking valproate, compared to two out of 144 women, or 1.4%, not taking valproate, developed PCOS in comparison to an estimated 5% rate in the general population.[26] In a follow-up study of these women, Joffe *et al*. found that PCOS symptoms remitted in three out of four women who discontinued valproate. In addition, menstrual cycle irregularities improved, and there was a trend toward lower serum testosterone among the women who discontinued valproate.[27] However, recent studies argue that these studies did not carefully assess the number of subjects who had reproductive abnormalities before diagnosis or treatment and have clarified it further. Rasgon *et al*., in a pilot study, investigated reproductive function in 22 female outpatients, aged between 18 and 45 years, taking lithium or divalproex sodium (Depakote) for a DSM-IV diagnosis of BPAD, and did not find any biochemical or radiological (ultrasound) evidence of PCOS. However, independent of therapeutic agent used, the bipolar women in this study reported high rates of menstrual disturbances.[6,9,26,28-30] These findings were further confirmed in their subsequent study, in which the authors report that four (5.5%) of 72 bipolar women had PCOS, three women met criteria for PCOS since treatment, and one woman reported a history of PCOS before treatment, which persisted into treatment.[5] Rasgon *et al*. emphasized on the contribution of dysregulation of the HPG axis in the clinical endophenotype of BPAD in women and suggested that women with BPAD may have neuroendocrine and menstrual dysregulation due to psychiatric illness before disease, increasing their susceptibility to aggravated abnormalities following psychotropic treatment.[5] And indeed, subsequent studies from several sources have documented HPG dysfunction in a proportion of the women with BPAD.[6,9,26,29,30] Furthermore, retrospective chart reviews in 189 women indicated that treatment with valproate did not appear to be a risk factor for the development of PCOS in patients with BPAD (Sachs, unpublished data).

In our study, the prevalence of PCOS was 27.9% among patients who had no history of valproate intake anytime during their illness, while it was 19.3% among patients who had taken valproate. Moreover, the mean duration of valproate intake was greater in the group with no PCOS (13.09 ± 18.61 months) as compared to group with PCOS (7.89 ± 14.12 months). We also found a statistically insignificant difference ($P = 0.07$) in the prevalence of PCOS among various drug groups (including the group on multiple mood stabilizers), classified on the basis of treatment at the time of assessment.

It is possible that those PCO-like changes occur in association with drugs only after years of exposure and that a false-negative result was obtained in the current study due to a relatively short length of exposure. In the index study by Isojärvi *et al*.,[7] the mean duration of therapy varied between 8 and 14 years in various drug groups while the mean duration of treatment in our study was 3.6 ± 4.36 years. In addition, in the study of Isojärvi *et al*., endocrinal effects of valproate use were most common among women who initiated treatment before the age of 20.[7] The majority of women in the current study began valproate treatment after the age of 20 years. It is possible that bipolar women are at increased risk for reproductive endocrinal changes when treatment begins during the adolescent years and/or are treated for longer lengths of time than in the current study. The impact of both length and timing of exposure to valproate on reproductive functioning require further study with larger sample sizes, longitudinal designs, and longer lengths of exposure.

Isojärvi *et al*. suggested that the overrepresentation of PCOS among valproate-treated women with epilepsy may be attributable to valproate-induced weight gain and the resultant endocrine concomitants of IR (hyperinsulinemia, increased insulin-like growth factor and decreased insulin-like growth factor-binding protein, and sex hormone-binding globulin). These endocrine changes increase gonadal steroidogenesis and permit a greater proportion of the released serum testosterone to be bioactive. Increased bioactive androgen may act locally in the ovary to block ovulation or may accomplish this through aromatization to estrogen and negative feedback on FSH secretion.

It was further suggested that there is possibility that epilepsy may promote PCOS and that PCOS is treated by most enzyme-inducing antiepileptic drugs but not by enzyme-inhibiting drugs such as valproate. Most commonly used antiepileptic drugs, including barbiturates, phenytoin, and carbamazepine, induce cytochrome P-450 and accelerate hepatic biotransformation, whereas valproate does not. Antiepileptic drugs that induce hepatic enzymes reduce biologically active testosterone levels in the serum by increasing the binding and metabolism of testosterone. Antiepileptic drugs other than valproate, therefore, may treat hyperandrogenism and thus PCOS, whereas valproate therapy may not. This mechanism thereby could also contribute to a higher occurrence of PCOS in valproate-treated women with epilepsy.[7,8] Since most of the antiepileptic drugs are used as mood stabilizers, the association between drug intake and BPAD can be similarly understood.

Although PCO is no longer deemed necessary for the diagnosis of PCOS, they represent arrest in antral follicle development and in many cases anovulation.[31] In our study, 27% of the patients had PCO on ultrasonography, of which 24% had bilateral PCO and 3% had unilateral PCO. Polson *et al*,[32] have reported PCO in 23% of a series of volunteers recruited among British hospital employees and Clayton *et al*,[33] identified a similar proportion of women as having PCO, specifically 22%. Similarly, Zargar *et al*. found 37.6% of the healthy control group having PCO.[25] However, the mean age of their control group was higher (34.98 ± 4.60) as compared to our study (24.96 ± 6.6). 48.14% of the patients having PCO on ultrasonography in our study had history of valproate intake. Our results are comparable to the results of other similar studies. Isojärvi *et al*. studied 238 women with epilepsy and found that 43% of the women receiving valproate had PCO and 50% of the women receiving valproate and carbamazepine had PCO.[7]

Further, 45% of our study population had a history of menstrual irregularities, of which 28% had oligomenorrhea, 16% had polymenorrhea, and 1% secondary amenorrhea. 48.8% of the patients having menstrual irregularity had a history of valproate intake. This is in accordance with various studies that show a positive correlation between valproate and menstrual disturbances. This association was first reported by Isojärvi *et al*., who studied 238 women with epilepsy and found that menstrual disturbances were present in 45% of the women taking valproate.[7] It was further confirmed by O'Donovan *et al.* who surveyed medical, psychiatric, and reproductive health history of 140 outpatient women with a DSM-IV diagnosis of bipolar disorder (aged 15–45 years) and found that significantly more women reported menstrual abnormalities in the valproate group (47%) than women not receiving valproate (13%) and controls (0%).[9] Independent studies by McIntyre *et al.*[34] and Joffe *et al.*[27,29] replicated similar results and suggested that valproate may, in some predisposed females, adversely impact upon the reproductive endocrine milieu and result in aspects of the metabolic syndrome. More recently, in a cross-sectional, multisite Stanley Foundation Bipolar Network study of eighty women with BPAD, Rasgon *et al*. found a 65% rate of current menstrual abnormalities, half of which also preceded BPAD diagnosis and treatment. Of the women who reported any (current and previous) menstrual abnormalities after initiating pharmacological treatment for BPAD (n = 15, or 38%), all but one woman reported developing menstrual abnormalities after initiation of treatment with valproate.[5]

In the current study, 54% of subjects had BMI ≥25. Similarly, women in studies by O'Donovan *et al*.[9] and McIntyre *et al*.[34] had mean BMI ≥25, and no differences in BMI were observed among treatment groups. Lack of BMI differences across studies, and independence of this finding from the type of treatment, suggests further that weight gain and obesity are common phenomena among women treated for bipolar disorder.[35,36] The medical implications of weight gain for our subjects should be taken into consideration. Taken together, the findings of a high frequency of menstrual abnormalities and overweight/obesity among women with bipolar disorder suggest vulnerability to long-term general health sequelae such as diabetes and cardiovascular disease. Studies have suggested an association between menstrual abnormalities and an increased risk for diabetes and cardiovascular disease, which is independent of obesity. Solomon *et al*. reported that healthy women with long or highly irregular menstrual cycles have a significantly increased risk for developing Type 2 diabetes that was not completely explained by obesity.[37] In another study by Cooper *et al*., however, longer bleeding periods in the mid and late reproductive years were only moderately associated with an increased risk of diabetes (adjusted rate ratio 1.4, 95% confidence interval 1.0–1.8 per day increase in bleeding duration for menses during ages 24–28).[38]

Statistically significant difference in prevalence of PCOS was found between rural and urban areas in our study, with urban areas showing higher prevalence. These results are not surprising as PCOS is largely considered as a lifestyle-related disease and has been attributed to a rapid nutritional transition toward an obesogenic diet and lifestyle which has become a norm in urban areas.[39] Along with the influences of western

lifestyle, recent shifts in cultural ideologies of what is expected of young urban women have changed. For women of reproductive age, an emphasis on being a "new Indian woman" requires an important balance of negotiating Western trends and new ideals with traditional customs and behaviors.[40-42]

CONCLUSION

The results from this study suggest that:

1. Although lack of community studies in this part of the world precludes proper comparisons, the rates of PCOS among bipolar women are high, regardless of the medication type
2. Lack of association with type and duration of treatment suggest that the PCOS arises out of the basic illness rather than as a complication of its treatment
3. Women with preexisting menstrual abnormalities may represent a group at risk for further endocrine dysfunction while treated for the disorder. Prospective, longitudinal studies will be better able to define the natural history of ovulatory function before and after introduction and discontinuation of valproate and other medications
4. Women with bipolar disorder appear to have not only reproductive abnormalities that may contribute to fertility problems but also metabolic abnormalities that may contribute to long-term medical comorbidity.

Limitations

There were a few limitations in our study.

- It was a hospital-based study which may not be representative of the individuals with less complex presentations in the community
- The cross-sectional design does not allow us to discern potential changes with time on concurrent medications or changes in menstrual patterns that can occur as a result of changing medications. In addition, it is quite possible that the women reporting menstrual disturbances were put on a safer medication by treating clinician at the outset of treatment leading to misattribution in our study. Effects of an individual medication are difficult to determine in an illness such as bipolar disorder, in which individuals are likely to have taken multiple medications over the course of the illness. Studies evaluating this phenomenon in newly diagnosed women with bipolar disorder receiving treatments *de novo* will be better able to disentangle specific drug effects
- The study design does not allow the separation of the effects of the disorder *per se* from the effects of the treatment agents
- The retrospective nature of some components of this study is a limitation in that women may over report or miss information related to duration and type of drug intake, course of illness, etc.
- Diet history was not taken because of which important information has been missed which might have contributed to metabolic abnormalities directly and hormonal abnormalities indirectly.

Recommendations

We recommend initial assessment of reproductive and metabolic endocrine status of all women diagnosed with bipolar disorder before treatment. During treatment, regular monitoring of weight and endocrine status should be done in all patients. If an endocrine disorder develops, the role of current medication should be assessed. Development of menstrual abnormalities may not constitute a reproductive disorder but should alert the treating clinician for closer monitoring. Early detection and prompt treatment can to a large extent prevent morbidity and mortality. Therapeutic lifestyle modification, healthy food habits, maintenance of high level of physical activity and normal weight, and family education about PCOS are most important strategies which can improve quality of life in these women.

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Conflicts of interest

There are no conflicts of interest.

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