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Evaluation of reproductive function in women treated for bipolar disorder compared to healthy controls

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Abstract

Objectives—The purpose of this study was to investigate the reproductive function of women with bipolar disorder (BD) compared to healthy controls.

Methods—Women diagnosed with BD and healthy controls with no psychiatric history ages 18 to 45 years were recruited from a university clinic and surrounding community. Participants completed a baseline reproductive health questionnaire, serum hormone assessment, and ovulation tracking for three consecutive cycles using urine luteinizing hormone (LH)-detecting strips with a confirmatory luteal-phase serum progesterone.

Results—Women with BD ($n = 103$) did not differ from controls ($n = 36$) in demographics, rates of menstrual abnormalities (MA), or number of ovulation-positive cycles. Of the women with BD, 17% reported a current MA and 39% reported a past MA. Dehydroepiandrosterone sulfate and 17-hydroxyprogesterone were higher in controls ($p = 0.052$ and 0.004 , respectively), otherwise there were no differences in biochemical levels. Medication type, dose, or duration was not associated with MA or biochemical markers, except those currently taking an atypical antipsychotic indicated a greater rate of current or past MA (80% versus 55%, $p = 0.013$). In women with BD, 22% reported a period of amenorrhea associated with exercising or stress, versus 8% of controls ($p = 0.064$). Self-reported rates of bulimia and anorexia nervosa were 10% and 5%, respectively.

Conclusions—Rates of MA and biochemical levels did not significantly differ between women with BD and controls. Current atypical antipsychotic use was associated with a higher rate of current or past MA and should be further investigated. Incidence of stress-induced amenorrhea should be further investigated in this population, as should comorbid incidence of eating disorders.

Keywords

bipolar disorder; eating disorder; hormones; menstrual abnormalities; polycystic ovary syndrome; reproductive function; women

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The reproductive function of women with bipolar disorder (BD) is of increasing interest to clinicians and patients alike. Previous studies have suggested that some medications used to treat BD, particularly anti-epileptic drugs (AEDs) such as valproate (VPA), are associated with a higher incidence of menstrual abnormalities (MA) and polycystic ovary syndrome (PCOS) (1–6), a poorly understood endocrine disorder characterized by chronic anovulation and hyperandrogenism (7). However, there has been some disagreement in the literature regarding this association (8–12). In women with epilepsy treated with AEDs, it has been proposed that reproductive dysfunction may be influenced by both medications and the neuroendocrine effects of epilepsy itself (13, 14). A similar question has been raised in the population of women with BD, given that the neuroendocrine systems are central to both reproductive function and mood disorders (15). In addition, individuals with BD 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 (16–18).

PCOS is one of the most common endocrine disorders in women, with an estimated incidence between 4% and 6% (19–21). In addition to being one of the most common causes of anovulatory infertility, PCOS is associated with an increased risk for type 2 diabetes, impaired glucose utilization, and cardiovascular disease (22–24). The standardized definition of PCOS has evolved over time and has varied in literature before the development of the standardized Rotterdam criteria (last revised in 2003), which proposed that PCOS be diagnosed based on fulfilling two of the following three criteria: oligomenorrhea or amenorrhea, clinical and/or biochemical hyperandrogenism, and polycystic ovaries (25). This has led to some disagreement as it has been argued that these criteria are not robust enough to support discerning clinical research (26–29). For example, the Androgen Excess Society regards hyperandrogenism as necessary for a diagnosis, along with either anovulation or polycystic ovary morphology (30).

We have previously reported high rates of MAs in women with BD, around 40% of whom report a current or previous MA (31–33), similar to rates published by others (5, 34). We have also reported cases of MA associated with VPA use in a cross-sectional study design (31), with length of VPA exposure being significantly associated with free testosterone levels and VPA use being associated with an increase over time in total testosterone in a longitudinal study setting (32). However, no studies to our knowledge have been able to compare these rates to a control population. Similarly, no studies have integrated an objective, longitudinal determination of ovulation simultaneously with self-report measures of menstrual cycle length. This study aimed to bring together cross-sectional biochemical assessments, self-report questionnaire data regarding reproductive functioning, and longitudinal, prospective ovulation tracking in women with BD and compare these measures of reproductive function to a control group of healthy women with no psychiatric history.

Methods

Participants

Women with BD between the ages of 18 and 45 years were recruited from the Center for Neuroscience in Women's Health and the Bipolar Disorders Clinic in the Department of Psychiatry and Behavioral Sciences at Stanford University Medical Center (Stanford, CA, USA), as well as from the surrounding community using fliers, advertisements in local newspapers, and through the registry of federally supported clinical trials (<http://clinicaltrials.gov>). Control subjects were recruited from the community using fliers and advertisements in local newspapers referencing a study on reproductive function. Control subjects with any history of psychiatric illness or history of ever having received psychotropic medication were excluded from the study. Exclusion criteria for all participants

included illicit drug use in the past six months; uncontrolled medical conditions; peri- or post-menopause [as indicated by follicle stimulating hormone (FSH) ≥ 40 mIU/mL]; hormonal contraceptive use within the past three months; current pregnancy, breast-feeding, or plans to get pregnant; endocrine disease (i.e., diabetes, hypothyroidism); or a mood disorder secondary to general medical condition. Diagnosis of BD was confirmed via administration of the Structured Clinical Interview for DSM-IV Diagnoses (SCID). Women with BD receiving psychotropic medication were required to have stable medications for at least three months prior to baseline evaluation.

Enrollment numbers for the study called for a 2:1 ratio of women with BD to healthy control subjects based on preliminary reproductive endocrine findings (11, 33) and a high projected rate of drop-out for women with BD. A total of 278 women with BD and 52 healthy female control subjects underwent an initial phone screen for eligibility. Forty women (14%) with BD declined to further participate and 102 (37%) failed telephone screening (32 due to unstable medications, 14 due to suicidal ideation, eight due to uncontrolled medical conditions or endocrine disease, 21 due to recent illicit drug use, 23 due to current breastfeeding or plans to get pregnant, and four due to perimenopause status). There were four (8%) healthy female control subjects who declined participation and eight (15%) who failed telephone screening (two due to psychiatric history, three due to plans to get pregnant, two due to recent illicit drug use, and one due to endocrine disease). Thus, 136 women with BD (49%) and 40 controls (77%) were consented into the study. A total of 121 women with BD (89%) and 38 controls (87%) completed the baseline intake evaluation and questionnaires, and 103 women with BD (76%) and 36 controls (90%) completed the assessment of metabolic function (See Fig. 1).

Procedures

All study evaluations took place at the Center for Neuroscience in Women's Health within the Department of Psychiatry and Behavioral Sciences at Stanford University Medical Center and at the Clinical Trials Research Unit (CTRU) at Stanford Hospital. After providing verbal and written informed consent, all subjects underwent the SCID to verify the psychiatric diagnosis of BD and to rule out psychopathology in control subjects. Assessment of eligibility also included a baseline screen of serum markers including FSH, thyroid function markers [thyroid stimulating hormone (TSH), T3, and T4], fasting insulin and glucose, and mood stabilizer (MS) levels to assess medication compliance; a urine toxicology screening and a urine HCG to rule out pregnancy; and the collection of a medical history to rule out uncontrolled medical conditions. Detailed information was collected from all patients with BD regarding current and previous psychotropic treatment. Where available, these data were cross-checked with clinic charts to ensure validity. Participants were required to notify study personnel of any medication changes.

After confirmation of eligibility, a trained clinical interviewer rated each subject on the Montgomery-Åsberg Depression Rating Scale (MADRS) (35) and the Young Mania Rating Scale (YMRS) (36) to assess the severity of current depressive and manic symptoms, and additional baseline data was collected including assessment of height, weight, and waist circumference; clinical assessment of hirsutism using the Ferriman-Gallwey scale (37); serum levels of bioavailable, free, and total testosterone; sex hormone binding globulin (SHBG); estradiol and estrone; luteinizing hormone (LH); FSH; 17-hydroxyprogesterone (17-OHP); dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS); prolactin; early morning fasting plasma glucose (FPG) and insulin (FPI). Glucose was measured with the glucose oxidase method on a YSI glucose analyzer (YSI Life Sciences, Yellow Springs, OH, USA), while the remaining serum markers were measured using the radio-immunoassay method by Diagnostic Systems Laboratories. PCOS was determined by the Revised 2003 Rotterdam criteria using self-report information on oligomenorrhea and

amenorrhea, the clinical Ferriman-Gallwey score, and the biochemical assessment of hyperandrogenism (free and total testosterone). When self-report data regarding polycystic ovarian morphology on ultrasound was available, this was also used. A detailed analysis of metabolic parameters in this sample—including body-mass index (BMI), waist circumference, FPG, and FPI—are presented elsewhere (24).

Subjects then completed three consecutive months of ovulation tracking using daily urine LH-surge ovulation tracking kits (American Screening Corporation, Shreveport, LA, USA) starting on Day 8 of their menstrual cycle. Subjects with a detectable LH surge underwent a midluteal phase confirmatory blood draw assessing progesterone five to seven days post-LH surge. Patients without a detectable LH surge underwent a progesterone blood draw between Days 19–21 of their menstrual cycle. For patients with amenorrhea or without a regular menstrual cycle, three consecutive monthly blood draws on the same day each month were obtained to assess progesterone. The study was approved in its entirety by the Stanford University Administrative Panel on Human Subjects. Subjects provided written and verbal informed consent prior to participation.

Statistical analysis

Statistical analyses were performed using SPSS software version 18.0 (SPSS, Inc., Chicago, IL, USA). All statistical tests were two-tailed and conducted at the 0.05 significance level. Statistical trends $p < 0.10$ were also noted. Univariate analysis of variance (ANOVA) and chi-square analyses were conducted to compare continuous and categorical data between BD and control participants as well as within subgroups of women with BD. Linear regression modeling was used to assess predictors of MA status and biochemical levels. Pearson correlation scores were used to assess correlation between continuous variables such as BMI and biochemical levels.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics for women with BD versus healthy controls are shown in Table 1. Women with BD did not significantly differ from healthy control participants in terms of age, years of education, distribution of ethnicity, marital status, or parity. Predictably, MADRS and YMRS scores were significantly higher for women with BD. Women with BD had a mean age of diagnosis at 26.8 years (range 9–41) and recorded a mean age of symptom onset (first depressive, manic, or hypomanic episode) of 15.8 years (standard deviation = 5.7, range 5–30). Rates of past use of oral contraceptives were similar between the two groups (90% in women with BD, 81% in controls).

Approximately three-fourths of patients with BD were euthymic at baseline evaluation using MADRS and YMRS scores (data not shown). Clinically significant depressive symptoms (MADRS score ≥ 20) were observed in 17.8% of women with BD. Clinically significant hypomanic symptoms (YMRS score between 12 and 19) were observed in 7.7% of women with BD, and clinically significant manic symptoms (YMRS score > 20) were observed in 1.1% of women with BD.

Among women with BD, 43% were receiving MS monotherapy, 15% AAP monotherapy, 25% MS + AAP combination therapy, and 7% antidepressant monotherapy, while 7% were medication-free for at least six months prior to study entry. Only two women with BD were completely treatment-naïve at study entry. Mood stabilizers included VPA, lithium (Li), carbamazepine, oxcarbazepine, and lamotrigine (LTG). Ten women with BD were receiving VPA, four of whom were on VPA monotherapy. In contrast, 17 women with BD were receiving Li, nine of whom were on Li monotherapy.

Menstrual history questionnaire data

Questionnaire data regarding menstrual history and abnormalities in women with BD versus healthy controls is presented in Table 2. Reported rates of MA, defined as oligomenorrhea (less than eight cycles in 12 months) or amenorrhea (no cycles for at least one year) did not differ between BD and controls. Among women with BD, 17% reported a current MA, 39% reported a past history of oligomenorrhea or amenorrhea but no current MA, and 36% reported no history of or current MA. Notably, of the 54 participants with BD who indicated a past or current MA, 23 (42.6%) reported a MA before diagnosis of BD. Similarly, of the 14 women with BD reporting a current MA, nine (64.3%) indicated having an MA before BD diagnosis. Five women with BD (4.7%) qualified for a diagnosis of PCOS using the Revised 2003 Rotterdam criteria, while none of the control subjects qualified (Table 2).

Among controls, incidence of current MA was 4%, history of MA was 34%, and no current or past MA was 53%. Subdivisions of oligomenorrhea and amenorrhea are further compared in Table 2, as well as additional data querying whether participants had experienced menstrual cycles shorter than 25 days or menstrual bleeding greater than 10 consecutive days. These rates did not significantly differ between BD and controls, though there was a trend toward more women with BD experiencing greater than 10 days of menstrual bleeding ($p = 0.009$). Mood rating scores on the MADRS and YMRS did not differ significantly between MA groups.

History of MA (either past or current) was also compared between types of BD [type I, type II, not otherwise specified (NOS)]. Thirty out of 37 women (81%) with BD type I indicated a current or past MA, versus 25 out of 38 women (66%) with BD type II, and 13 out of 22 (59%) women with BD NOS, however these differences were not statistically significant ($p = 0.154$). Current or past history of MA was not associated with clinically assessed weight, BMI, scores on MADRS or YMRS, age at diagnosis of BD, age at first manic episode, or age at first depressive episode.

Seven women with BD self-identified on questionnaire as having been diagnosed previously with anorexia nervosa, while 10 self-identified as having been diagnosed with bulimia nervosa. In women with BD, 21 out of 96 women (22%) marked that they had experienced a period of time during which they had stopped having periods due to stress or exercise, versus three out of 37 controls (8%) ($p = 0.064$).

Ovulation tracking

Regarding ovulation tracking data, 59 of the 103 women with BD underwent at least one month of luteal progesterone assessment to evaluate ovulation. Of these 59, 50 underwent two consecutive months of testing and 48 underwent three consecutive months. In comparison, 33 of the control women underwent testing during the first month, 30 of these women underwent two consecutive months, and 28 underwent three consecutive months (see Fig. 1). For purposes of comparison between BD and controls, the five women with diagnosed PCOS were excluded from analysis. Data regarding rate of ovulation is presented in Table 3 and did not differ between BD and controls. Ovulation tracking data was also aggregated by current MA, past MA, or no history of MA. Among those with BD, 57% of those reporting a current MA demonstrated two ovulatory cycles, compared to 86% of those with a past MA and 94% of those with no MA; however, cell sizes were small and statistical analysis did not find any significant difference between these rates. In control women, all three women who indicated a current MA had two ovulatory cycles, compared to 90% of women with a past MA and 81% of women with no MA.

Biochemical data

Data comparing biochemical levels of reproductive hormones between those with BD and healthy controls are presented in Table 4. Values were not significantly different except for DHEAS (higher in controls, $p = 0.052$) and 17-OHP (higher in controls, $p = 0.004$).

Biochemical data was further compared among women with BD by MA status (current, past, none) and BD diagnosis (type I, type II, and NOS) (data not shown). In comparing the three MA subgroups, LH:FSH ratio was notably highest in those with a current MA, and lowest in those with no history ($p = 0.046$). Similarly, SHBG was lowest in those with no history of MA, but did not separate out in those with current or past MA ($p = 0.010$).

When comparing biochemical data by BD diagnosis, significant differences were noted in DHEAS and 17-OHP. DHEAS was significantly higher in BD type I and BD type II when compared to BD NOS (200 ± 117.0 , 187 ± 97.2 , and 137 ± 49.2 , respectively; $p = 0.013$). Similarly, 17-OHP was noted to be highest in BD type I and lowest in BD NOS (66.0 ± 56.6 , 63.7 ± 51.4 , and 53.1 ± 31.3 ; $p = 0.036$).

Data regarding metabolic biochemical parameters and familial history of diabetes is published elsewhere (24). BMI was not correlated with most biochemical measures except negatively with SHBG (Pearson correlation of -0.234 , $p = 0.018$), a finding that was not mediated by MA history or BD diagnosis. BMI was also not significantly different among the three MA subgroups.

Medication data

Presence and history of MA, number of positive ovulations, and biochemical data were compared between women with BD who had been on psychotropic medication for less than three months (including the two treatment-naïve patients, total $n = 32$) versus those who had been on psychotropic medications greater than three months ($n = 87$, three subjects with missing data). Fifty-three percent ($n = 17$) of those on medications less than three months indicated no current or past MA, versus only 27% ($n = 18$) in women on medications for greater than three months, however this was not significantly different ($p = 0.108$). For women with at least two months of ovulation data, 75% ($n = 12$) of those on less than three months of medication had at least two positive ovulations, compared to 83% ($n = 30$) of women on medication greater than three months (not significant). Of those with three months of ovulation data, 42% of women with BD on less than three months of medication had three ovulation positive cycles compared to 40% of those on medications for greater than three months (not significant). There were no significant differences in any biochemical markers between treatment duration groups.

In women with BD, MA status (current, past, never), number of positive ovulations, and biochemical data were also compared between those currently or ever on VPA, Li, or an AAP. No differences in MA status or number of positive ovulations were noted between women currently on VPA (versus those who were not) or between women ever on VPA (versus those who were not). Similarly, no differences were noted between the Li treatment groups. However, 80% (20 out of 25) of women who were currently taking an AAP indicated a current or past MA, versus 55% (37 out of 67) of women not currently taking an AAP ($p = 0.013$). Past use of AAPs was not recorded. Using linear regression, number of months on AAP did not predict MA status. Ovulation and biochemical data did not differ between those who were currently or ever taking VPA or an AAP compared to those who had not. For women with BD indicating that they were either currently taking or had ever taken Li, mean follicular phase estrone was significantly higher (59.2 ± 17.6 versus 46.2 ± 13.5 , $p = 0.002$), no other differences were noted. Linear regression did not indicate a significant factor of Li-use duration.

Discussion

The reproductive function of women with BD has increasingly become an area of interest, driven by the need to clarify the risks and benefits of medication regimens in order to drive better treatment guidelines. However, much remains to be elucidated; for example, few studies describe even baseline levels of reproductive hormones or self-report MAs in this population, and virtually no studies have compared reproductive indices in women with BD to active controls. In addition, it is poorly understood whether reproductive function may be impacted by the pathophysiology of BD itself, perhaps through modulations of the hypothalamic-pituitary-adrenal (HPA)/hypothalamic-pituitary-gonadal (HPG) axes, versus potential effects of medications used to treat BD, such as VPA, Li, and increasingly AAPs. Medications that have been implicated include the possible effect of VPA on testosterone and insulin resistance in the development of PCOS (1, 3–5) and the metabolic effects of AAPs, which may also mediate the development of anovulatory syndromes such as PCOS, though the studies remain divided (8–12).

To our knowledge, this is the first published study that has examined reproductive function in women with BD in comparison to a control population. In this clinical sample, the self-reported rate of oligomenorrhea or amenorrhea was close to 40%, consistent with our own previously reported rates in a longitudinal evaluation of reproductive function in 25 women with BD (which represented a different sample using similar enrollment criteria) (32) as well as rates published by others (5, 34). Also consistent with our 2005 findings, we found that rates of oligomenorrhea and amenorrhea did not differ between treatment groups, including those who had been treated for less than three months or not at all, and that many patients noted a MA that preceded the diagnosis of BD, and therefore the treatment of BD (32).

It is interesting to note that reported rates of MA in our current study did not necessarily correlate with anovulation as measured by three consecutive monthly luteal-phase progesterone levels, nor did they reflect the relatively low rate of PCOS at around 5%, which matches the normal population rate of 4–6% (20, 21), though few studies reflect the most updated Rotterdam criteria. The majority of patients (almost 90%) had at least two positive ovulations during the consecutive three months, and this did not differ between women with BD and controls, nor did it differ significantly by MA status. Notably, only 57% of our participants with BD completed even one month of the ovulation tracking, which speaks to the feasibility constraints of tracking, liaising, and coordinating with necessary precision in this population. Though the exact reasons that participants were unable to complete ovulation tracking were not assessed, many of the women with BD in our study were either students or worked part- or full-time, presenting significant scheduling difficulties. However this was similarly true for the majority of our control participants, of which 92% completed at least one ovulation tracking cycle, which may speak to the unique motivations of the largely self-selected control population. Additionally, there may have been self-selection bias within the control population, given that recruitment efforts made reference to assessment of reproductive function, but the direction of this bias is unclear as reasons to participate in such a study could vary. Though the percentage of women with BD who obtained ovulation tracking data is low, this study was able to retain most of those subjects over the three-month tracking period, with an attrition rate of 19%.

It is unclear why self-reported rates of MA, specifically oligomenorrhea and amenorrhea do not match up with objectively measured ovulation rates. This may reflect a perceived experience of variability in the menstrual cycle with a retrospective reporting bias that appears to be similar in both women with BD and controls but that does not necessarily reflect current ovulatory functioning. This finding points to a future need to assess closely

for objective measures of reproductive functioning, such as biochemical ovulation tracking rather than relying on self-report menstrual cycle questionnaires.

Almost 10% of women with BD self-reported a diagnosis of bulimia nervosa, with 5% reporting a diagnosis of anorexia nervosa. Given that this study selected a control group without a psychiatric diagnosis, we cannot compare these two populations in our study, however this data adds to a sparse but growing literature on the prevalence of eating disorders in women with BD (38–40). A recent study by McElroy et al. (41) reported a rate of binge eating disorder in women with BD to be 9%, compared to 5% for bulimia nervosa and 3% for anorexia nervosa, for an overall rate of 14.3% for all eating disorders. In our study we did not specify between binge-eating disorder and bulimia, however our preliminary rates do appear to be similar to these reported rates. They are also similar to rates reported in a subgroup analysis comparing men and women with BD in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, which found significantly higher rates of reported bulimia in women (12%) compared to men (2%) (42). Further exploration of the intersection of BD and eating disorders is needed, particularly in light of the growing consensus that certain eating disorders may share neurocircuitry with dysregulated impulse control (43).

Twenty-two percent of women with BD indicated that they had experienced a period of time during which they stopped having periods due to stress or exercise, versus 8% of controls, though this represents retrospective self-report data. This incidence of what is sometimes called hypothalamic or central amenorrhea due to the surmised central role of HPA dysregulation (44) has not, to our knowledge been reported in the BD population to date. However, this preliminary data suggests that it should be further investigated, particularly as we continue seeking to understand how the HPA and HPG axes function in the context of BD and its pharmacotherapy.

In fact, these rates of self-reported eating disorders and central amenorrhea may help to explain the high rates of reported past MA in the BD population. Particularly if the eating disorder or period of exercise or stress was in the past, resolution of the MA would occur with resolution of the disorder and may explain why past MA was far more commonly reported than current MA, or even why current MAs were at times accompanied by normal ovulation tracking results. However, these aspects of the potential inter-relatedness of eating disorders, central amenorrhea, and BD deserve further careful longitudinal study for clarification.

Interestingly, DHEAS and 17-OH-progesterone were both significantly higher in controls compared to patients with BD. Increased DHEAS and 17-OH-progesterone values, as general indicators of adrenal function, have been associated with states of HPA and HPG dysregulation, such as PCOS (45), however rates of PCOS or MA were not higher in controls. However, given the higher reporting of past central amenorrhea in women with BD, the lower DHEAS and 17-OH-progesterone values could represent an adrenal ‘burn-out’ scenario in which continued dysregulation at the level of the HPA axis eventually leads to lower adrenal hormone production. This theory remains speculation at this point and further studies are needed.

There has been considerable discussion in the literature regarding whether psychotropic medications, in particular those used as mood stabilizers, cause reproductive dysfunction or MAs such as PCOS. The use of VPA has been a particular point of interest, though the metabolic effects of AAPs have also caused growing concern. As reviewed in this 2008 publication (46), while many studies have shown an association between VPA use and MAs or biochemical abnormalities, not all have upheld this association. Similar to our previous

studies, we did not find any biochemical differences, including free or total testosterone between women receiving or not receiving VPA. However, in our previous studies we did find that duration of VPA use was positively correlated with free testosterone levels, something we could not corroborate in the current study. Notably, in this study we found that a higher percentage of women currently taking an AAP indicated a past or present MA compared to those not on an AAP, suggesting a future area for research as little as been published regarding the use of AAPs and reproductive dysfunction.

Regarding our population sample, clinical and demographic characteristics were similar in many ways to those reported in other large, multi-site studies in the BD population (47), though only one of these large studies completed a subset analysis comparing data by gender (42). In the latter study, investigators found that rates of BD type II were higher in women compared to men (30% compared to 16% respectively), a finding that had been noted in two previous studies but had not reached statistical significance (48, 49). Rates of BD NOS were not reported. Notably, our rates of women diagnosed with BD type II and BD NOS were higher than those previously cited, at 39% and 23%, respectively. It is unclear why BD type II and BD NOS patients were more highly represented in our sample, though given that women with BD generally self-selected to contact the study coordinator for enrollment in our study, it may reflect an increased drive toward study participation in these populations for unknown reasons. It is important to note that our sample population did not include women with uncontrolled medical conditions or illicit substance use, therefore the results may not be generalizable to these populations. It is also interesting to note the stability of our population is both a strength of the study as it avoids potential confounding effects of acute affective episodes (either depression or mania) and a weakness in that we were unable to explore whether changes in our biochemical variables are reflected in acute affective states.

Though it is the first study to compare reproductive function data in women with BD against a control group of healthy women, this study presents some limitations, particularly in the size and sampling of the control group, which could contribute to the lack of differences between groups for some variables. At the same time, the present study included a fairly large sample of women with BD ($n = 103$). The reason for the unequal numbers of women with BD to control women is that the original proposal was designed with a 2:1 ratio of women with BD to healthy controls for three-month ovulation tracking data as part of the overall metabolic and reproductive aims of the study. Given that a high dropout was projected for women with BD, a much larger number of women with BD underwent baseline function. As noted earlier, the control population was solicited through community advertisements, which led to a self-selected group of women who pursued enrollment, and it is possible that these women represent a unique population with a vested interest in obtaining information about their reproductive functioning, thus posing potential difficulties in generalizability. However the two groups were notably similar in terms of demographic information.

As in almost all studies of BD, a significant portion of patients with BD were receiving more than one psychotropic medication, and the absence of uniform treatment regimens represents a limitation of the results. Missing data and small cell sizes prevented analysis of some measures such as AAP dosing and presence of AAPs known to cause prolactinemia. At the same time, this study is a reflection of real-life treatment of BD, as no single treatment approach provides adequate outcomes for many of the diverse patients with this illness. It would also be relevant and important to include a measure of trauma history, which was not included in our assessment, given the prevalence of trauma in this population and its potential impact on neuroendocrine axes.

In summary, women with BD exhibit a high rate of current and past MA, but this rate does not appear to differ from the rate in control populations. Further studies investigating MAs should take into consideration the fact that many subjects who subjectively reported oligomenorrhea or amenorrhea had two out of three, if not three out of three positive ovulations during tracking, suggesting the need for more objective means of measuring menstrual functioning. Medications did not show associations with biochemical markers or objective evaluation of ovulation tracking, however current AAP use was associated with a higher rate of current or past MA. History of and/or current incidence of central amenorrhea due to HPA dysregulation should be further investigated in this population.

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References

1. Isojärvi JIT, Laatikainen TJ, Pakarinen AJ, Juntunen KTS, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med*. 1993; 329:1383–1388. [PubMed: 8413434]
2. Isojärvi JIT, Laatikainen TJ, Knip M, Pakarinen AJ, Juntunen KT, Myllylä VV. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996; 39:579–584. [PubMed: 8619542]
3. Morrell MJ, Isojärvi J, Taylor AE, et al. Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. *Epilepsy Res*. 2003; 54:189–199. [PubMed: 12837570]
4. McIntyre RS, Mancini DA, McCann S, Srinivasan J, Kennedy SH. Valproate, bipolar disorder and polycystic ovarian syndrome. *Bipolar Disord*. 2003; 5:28–35. [PubMed: 12656935]
5. O'Donovan C, Kusumakar V, Graves GR, Bird DC. Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder. *J Clin Psychiatry*. 2002; 63:322–330. [PubMed: 12000206]
6. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol*. 2004; 24:322–334. [PubMed: 15118487]
7. Dunaif A, Thomas A. Current concepts in the polycystic ovary syndrome. *Annu Rev Med*. 2001; 52:401–419. [PubMed: 11160786]
8. Bilo L, Meo R, Valentino R, Di Carlo C, Striano S, Nappi C. Characterization of reproductive endocrine disorders in women with epilepsy. *J Clin Endocrinol Metab*. 2001; 86:2950–2956. [PubMed: 11443149]
9. Bauer J, Jarre A, Klingmüller D, Elger CE. Polycystic ovary syndrome in patients with focal epilepsy: a study in 93 women. *Epilepsy Res*. 2000; 41:163–167. [PubMed: 10940617]
10. Murialdo G, Galimberti CA, Magri F, et al. Menstrual cycle and ovary alterations in women with epilepsy on antiepileptic therapy. *J Endocrinol Invest*. 1997; 20:519–526. [PubMed: 9413805]
11. Rasgon NL, Altshuler LL, Gudeman D, et al. Medication status and polycystic ovary syndrome in women with bipolar disorder: a preliminary report. *J Clin Psychiatry*. 2000; 61:173–178. [PubMed: 10817101]
12. Altshuler, LL.; Rasgon, N.; Elman, S., et al. Reproductive Endocrine Function in Women Treated for Bipolar Disorder: Reproductive Hormone Levels. New York: American Psychiatric Association; 2004.

13. Bilo L, Meo R. Polycystic ovary syndrome in women using valproate: a review. *Gynecol Endocrinol*. 2008; 24:562–570. [PubMed: 19012099]
14. Bauer J, Cooper-Mahkorn D. Reproductive dysfunction in women with epilepsy: menstrual cycle abnormalities, fertility, and polycystic ovary syndrome. *Int Rev Neurobiol*. 2008; 83:135–155. [PubMed: 18929079]
15. Newberg AR, Catapano LA, Zarate CA, Manji HK. Neurobiology of bipolar disorder. *Expert Rev Neurother*. 2008; 8:93–110. [PubMed: 18088203]
16. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999; 156:1686–1696. [PubMed: 10553730]
17. Haddad P. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol*. 2005; 19(Suppl. 6):16–27. [PubMed: 16280334]
18. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005; 19(Suppl. 1):1–93. [PubMed: 15998156]
19. Franks S. Polycystic ovary syndrome. *N Engl J Med*. 1995; 333:853–861. [PubMed: 7651477]
20. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab*. 1999; 84:4006–4011. [PubMed: 10566641]
21. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab*. 1998; 83:3078–3082. [PubMed: 9745406]
22. Wild RA, Carmina E, Diamanti-Kandarakis E, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab*. 2010; 95:2038–2049. [PubMed: 20375205]
23. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2010; 16:347–363. [PubMed: 20159883]
24. Rasgon NL, Kenna HA, Reynolds-May MF, et al. Metabolic dysfunction in women with bipolar disorder: the potential influence of family history of type 2 diabetes mellitus. *Bipolar Disord*. 2010; 12:504–513. [PubMed: 20712751]
25. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004; 19:41–47. [PubMed: 14688154]
26. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. *J Clin Endocrinol Metab*. 2006; 91:781–785. [PubMed: 16418211]
27. Franks S. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria. *J Clin Endocrinol Metab*. 2006; 91:786–789. [PubMed: 16418209]
28. Barth JH, Yasmin E, Balen AH. The diagnosis of polycystic ovary syndrome: the criteria are insufficiently robust for clinical research. *Clin Endocrinol*. 2007; 67:811–815.
29. Belosi C, Selvaggi L, Apa R, et al. Is the PCOS diagnosis solved by ESHRE/ASRM 2003 consensus or could it include ultrasound examination of the ovarian stroma? *Hum Reprod*. 2006; 21:3108–3115. [PubMed: 17053004]
30. Azziz R, Carmina E, Dewailly D, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006; 91:4237–4245. [PubMed: 16940456]
31. Rasgon NL, Altshuler LL, Fairbanks L, et al. Reproductive function and risk for PCOS in women treated for bipolar disorder. *Bipolar Disord*. 2005; 7:246–259. [PubMed: 15898962]
32. Rasgon NL, Reynolds MF, Elman S, et al. Longitudinal evaluation of reproductive function in women treated for bipolar disorder. *J Affect Disord*. 2005; 89:217–225. [PubMed: 16171873]
33. Rasgon N, Bauer M, Glenn T, Elman S, Whybrow PC. Menstrual cycle related mood changes in women with bipolar disorder. *Bipolar Disord*. 2003; 5:48–52. [PubMed: 12656938]

34. Akdeniz F, Taneli F, Noyan A, Yüncü Z, Vahip S. Valproate-associated reproductive and metabolic abnormalities: are epileptic women at greater risk than bipolar women? *Prog Neuropsychopharmacol and Biol Psychiatry*. 2003; 27:115–121. [PubMed: 12551733]
35. Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
36. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978; 133:429–435. [PubMed: 728692]
37. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*. 1961; 21:1440–1447. [PubMed: 13892577]
38. Fornaro M, Perugi G, Gabrielli F, et al. Lifetime co-morbidity with different subtypes of eating disorders in 148 females with bipolar disorders. *J Affect Disord*. 2010; 121:147–151. [PubMed: 19559486]
39. Wildes JE, Marcus MD, Fagioli A. Prevalence and correlates of eating disorder co-morbidity in patients with bipolar disorder. *Psychiatry Res*. 2008; 161:51–58. [PubMed: 18782643]
40. McElroy SL, Kotwal R, Keck PE Jr. Comorbidity of eating disorders with bipolar disorder and treatment implications. *Bipolar Disord*. 2006; 8:686–695. [PubMed: 17156155]
41. McElroy SL, Frye MA, Helleman G, et al. Prevalence and correlates of eating disorders in 875 patients with bipolar disorder. *J Affect Disord*. 2011; 128:191–198. [PubMed: 20674033]
42. Baldassano CF, Marangell LB, Gyulai L, et al. Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. *Bipolar Disord*. 2005; 7:465–470. [PubMed: 16176440]
43. Kaye WH, Wagner A, Fudge JL, Paulus M. Neurocircuitry of eating disorders. *Curr Top Behav Neurosci*. 2011; 6:37–57. [PubMed: 21243469]
44. Genazzani AD. Neuroendocrine aspects of amenorrhea related to stress. *Pediatr Endocrinol Rev*. 2005; 2:661–668. [PubMed: 16208279]
45. Azziz R, Black V, Hines GA, Fox LM, Boots LR. Adrenal androgen excess in the polycystic ovary syndrome: sensitivity and responsivity of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab*. 1998; 83:2317–2323. [PubMed: 9661602]
46. Joffe H, Hayes FJ. Menstrual cycle dysfunction associated with neurologic and psychiatric disorders: their treatment in adolescents. *Ann N Y Acad Sci*. 2008; 1135:219–229. [PubMed: 18574228]
47. Kogan JN, Otto MW, Bauer MS, et al. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Bipolar Disord*. 2004; 6:460–469. [PubMed: 15541061]
48. Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C. Gender and bipolar illness. *J Clin Psychiatry*. 2000; 61:393–396. [PubMed: 10847318]
49. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. *Acta Psychiatr Scand Suppl*. 1985; 317:1–34. [PubMed: 3861072]

Fig. 1.
Enrollment and attrition. BD = bipolar disorder.

Table 1

Demographic and clinical characteristics of women with bipolar disorder and healthy controls

	Bipolar disorder (n = 103)	Controls (n = 36)	p-value
Age, years, mean (SD)	31.9 (6.7)	31.3 (7.4)	NS
Education, years, mean (SD)	15.8 (1.7)	16.1 (1.7)	NS
Ethnicity, n (%)			
Caucasian	82 (79.6)	26 (66.7)	NS
Asian/Pacific Islander	9 (8.7)	5 (13.9)	NS
Hispanic	10 (9.7)	4 (11.1)	NS
African American	2 (1.9)	3 (8.3)	NS
Marital status, n (%)			
Single/divorced	51 (49.5)	22 (61.1)	NS
Married or living with partner	52 (50.4)	14 (38.9)	NS
Parity, mean (SD)	0.45 (0.87)	0.45 (0.81)	NS
MADRS score at study entry, mean (SD)	10.6 (8.7)	1.9 (2.9)	p < 0.001
YMRS score at study entry, mean (SD)	4.7 (4.5)	1.2 (1.9)	p < 0.001
Age at BD diagnosis, years, mean (SD)	26.8 (6.6)	N/A	
Type of BD, n (%)		N/A	
BD type I	37 (35.9)		
BD type II	40 (38.8)		
BD NOS	24 (23.3)		
Duration of MS/AAP use, months, n (%)		N/A	
< 3 months	17 (16.5)		
3–6 months	16 (15.5)		
6–12 months	20 (19.4)		
12+ months	33 (32.1)		
No MS/AAP in past 6 months	15 (14.5)		

SD = standard deviation; MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; BD = bipolar disorder; NOS = not otherwise specified; MS = mood stabilizer; AAP = atypical antipsychotic; NS = not significant; N/A = not applicable.

Table 2

Menstrual history questionnaire data for women with bipolar disorder and healthy controls

	Bipolar disorder (n = 103)	Controls (n = 36)	p-value
Self-report MA, n (%)			
No current or past history of MA	64 (62.0)	27 (75.0)	NS
History of oligomenorrhea	8 (7.8)	3 (8.3)	NS
History of amenorrhea	8 (7.8)	2 (5.5)	NS
Current oligomenorrhea	9 (8.7)	2 (5.5)	NS
Current amenorrhea	7 (6.8)	2 (5.5)	NS
Pre-existing MA prior to BD diagnosis, n (%)	26 (25.0)	–	–
PCOS diagnosis, n (%)	5 (4.8)	0 (0)	NS
Central amenorrhea, n (%)	22 (21.0)	4 (11.0)	NS
Age at menarche, years, mean (SD)	12.44 (1.47)	12.38 (1.52)	NS
No. of cycles in the last 12 months, mean (SD)	11.2 (1.96)	11.9 (1.37)	0.016 ^a
Menstrual cycle < 25 days, n (%)	24 (23.0)	9 (25.0)	NS
Bleeding > 10 days, n (%)	32 (31.0)	4 (11.0)	0.009
Body mass index, mean (SD)	27.5 (7.5)	24.8 (5.1)	0.035

MA = menstrual abnormality; BD = bipolar disorder; PCOS = polycystic ovary syndrome; SD = standard deviation; NS = not significant.

^aMann–Whitney *U*-test.

Table 3

Ovulation tracking data in bipolar disorder and healthy controls

	Bipolar disorder^a (n = 59, 50, 48)	Controls^a (n = 33, 30, 28)	p-value
Positive ovulation during, n (%)			
First cycle	38 (64)	25 (76)	NS
Second cycle	45 (90)	25 (76)	NS
Third cycle	35 (73)	19 (68)	NS
Positive ovulation for at least two cycles, n/n total (%) ^b	43/48 (89)	25/27 (92)	NS
Positive ovulation for all three cycles, n (%)	20 (42)	11 (39)	NS
No. who did not ovulate at all or only ovulated 1/3 consecutive cycles, n (%)	9 (19)	4 (14)	NS

NS = not significant.

^a n includes all women (except those with polycystic ovary syndrome) who obtained ovulation data for one, two, and three consecutive cycles, respectively.

^b n total = number of women with at least two cycles of data, minus women with only two cycles of data that were split between one positive and one negative result.

Table 4

Biochemical data in women with bipolar disorder and healthy controls

	Bipolar disorder		Controls		p-value
	Mean (SD)	N	Mean (SD)	N	
Prolactin	11.2 (8.4)	77	12.6 (7.2)	32	NS
Estradiol	44.2 (32.7)	78	38.8 (17.9)	34	NS
LH	5.6 (2.9)	78	5.1 (2.0)	33	NS
FSH	7.3 (6.1)	77	6.7 (1.8)	34	NS
FSH/LH ratio	0.9 (0.5)	77	0.8 (0.3)	33	NS
Estrone	53.6 (17.8)	73	54.6 (17.9)	33	NS
DHEAS	180.8 (98.9)	76	221.2 (102.0)	34	0.052
Free testosterone	3.7 (6.6)	76	3.0 (2.1)	34	NS
Total testosterone	31.5 (47.1)	76	23.0 (12.1)	34	NS
SHBG	57.6 (32.3)	71	53.2 (28.3)	34	NS
17-OHP	61.9 (48.8)	76	90.1 (40.7)	34	0.004
DHEA	9.1 (7.1)	67	9.7 (6.8)	32	NS

SD = standard deviation; LH = luteinizing hormone; FSH = follicle-stimulating hormone; DHEAS = dihydroepiandrosterone sulfate; SHBG = sex hormone binding globulin; 17-OHP = 17-hydroxyprogesterone; DHEA = dihydroepiandrosterone; NS = not significant.