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Hormonal Influence on Mood Dysregulation: A Case of Bipolar Disorder with Endometriosis

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ABSTRACT: Bipolar disorder often coexists with gynecological conditions such as endometriosis, presenting clinical challenges due to overlapping hormonal and neuropsychiatric influences. The impact of hormonal therapy on mood stability in women with affective disorders remains underexplored. We report the case of a 30-year-old woman with bipolar II disorder, stable for nearly two years on lamotrigine, who developed mood destabilization after initiating hormonal treatment for stage III endometriosis. Sequential regimens—dienogest, norethisterone, and ethinylestradiol–levonorgestrel—were temporally associated with new or worsening mixed affective symptoms, including agitation, insomnia, irritability, and emotional lability, despite adherence to mood stabilizers. Her Hamilton Depression Rating Scale score increased from 9 to 21 within three months, with laboratory evaluation showing elevated estradiol and suppressed luteinizing hormone, supporting a hormone-related mechanism. A structured literature review (PubMed, Scopus, Google Scholar, 2000–2024) identified limited but consistent evidence that synthetic progestins may exacerbate psychiatric symptoms in mood-vulnerable populations through neuroendocrine and neurotransmitter modulation. This case underscores the importance of recognizing hormonally induced mood dysregulation in women with pre-existing psychiatric disorders and highlights the need for proactive management strategies. We recommend pre-treatment psychiatric screening, structured and longitudinal mood monitoring throughout hormonal therapy, and close interdisciplinary collaboration between gynecology and psychiatry to optimize outcomes. Integrated care approaches may reduce the risk of mood destabilization, enhance safety, and improve quality of life for women facing the dual burden of bipolar disorder and endometriosis.

Keywords: Bipolar Disorder, Endometriosis, Hormonal Therapy, Mood Dysregulation, Women's Mental Health.

INTRODUCTION

Bipolar disorder is a chronic mood disorder characterized by extreme fluctuations in affective states, ranging from episodes of depression to hypomania or mania, and often necessitating long-term, multi-modal management. Intriguingly, this psychiatric condition is not infrequently observed in conjunction with chronic gynecological illnesses such as endometriosis. The coexistence of these two conditions is more than a coincidental finding; rather, it reflects an area of clinical overlap in which hormonal influences and neuropsychiatric mechanisms interact in complex and sometimes synergistic ways. The management of such comorbidity presents significant challenges, requiring the coordinated expertise of psychiatry, gynecology, endocrinology, and immunology.

This overlap is particularly relevant for women of reproductive age, a population in which both conditions reach peak prevalence. During this stage of life, women experience pronounced hormonal fluctuations—whether physiologically, as part of the menstrual cycle, pregnancy, and menopause, or iatrogenically, through the use of hormonal therapies. Such fluctuations can exert profound effects not only on reproductive health but also on emotional and cognitive functioning. Consequently, the care of women affected by both bipolar disorder and endometriosis must address not only the somatic manifestations of each condition but also the interplay between hormonal dynamics and psychiatric stability.

Epidemiological evidence consistently demonstrates that women are approximately twice as likely as men to develop depression. This gender disparity is thought to result from a complex interaction between hormonal, genetic, and psychosocial determinants (Kuehner, 2017). Reproductive hormones—especially estrogen and progesterone—are known to modulate key neurotransmitter systems, including serotonergic, dopaminergic, and GABAergic pathways, all of which play essential roles in mood regulation. Alterations in hormone levels, therefore, have the potential to destabilize emotional balance, particularly in individuals with pre-existing affective vulnerability, such as those with a diagnosis of bipolar disorder.

Despite the longstanding role of hormonal therapy as a mainstay in the management of endometriosis—used to alleviate pain, suppress ectopic endometrial tissue growth, and improve fertility outcomes—its capacity to disrupt mood stability in patients with mood disorders remains underexplored in systematic research. In clinical practice, hormonal regimens are frequently initiated in mood-vulnerable patients without the benefit of clear psychiatric guidelines or monitoring protocols (Bertollo et al., 2025). This absence of integrated oversight increases the likelihood of triggering affective relapse or exacerbation, thereby complicating the therapeutic course and impairing quality of life.

Endometriosis itself affects an estimated 10–15% of women of reproductive age worldwide. Beyond its hallmark symptoms of chronic pelvic pain, dysmenorrhea, and infertility, the condition is associated with substantial psychological distress (Laganà, 2020). The cumulative burden of recurrent pain, functional impairment, and uncertainty regarding reproductive potential can generate chronic stress, often intensifying pre-existing depressive or anxious symptoms.

Conversely, bipolar disorder affects approximately 1–3% of the global population, with prevalence rates consistently higher in females than in males (Rowland, 2021). Several biological mechanisms

are believed to contribute to the frequent co-occurrence of bipolar disorder and endometriosis. Hormonal fluctuations—particularly in estrogen and progesterone—can influence neurotransmission across mood-relevant systems (Barth et al., 2015; Schmidt, 2021). Estrogen, for instance, is implicated in modulating stress reactivity and emotional processing via its effects on neural networks governing executive control. According to the neurocognitive model proposed by Albert & Newhouse (2019), cyclical or abrupt changes in estrogen levels can disrupt the balance among serotonergic, dopaminergic, and glutamatergic systems, thereby heightening susceptibility to depressive symptoms, especially during periods of hormonal transition.

In addition to these neuroendocrine dynamics, endometriosis is associated with elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are capable of crossing the blood–brain barrier. Once in the central nervous system, these cytokines can alter neurotransmitter metabolism and modulate hypothalamic–pituitary–adrenal (HPA) axis responsiveness (Miller & Raison, 2016; Sherwani et al., 2024). This combination of hormonal variability and immune activation creates a neurobiological environment conducive to mood destabilization.

Furthermore, it is important to recognize that the intersection between bipolar disorder and endometriosis does not occur in isolation but rather within a broader biopsychosocial framework. Hormonal influences on mood are modulated not only by endocrine and neurochemical pathways but also by environmental stressors, lifestyle factors, and personal coping mechanisms. For example, the cyclical nature of endometriosis-related pain may impose recurrent functional limitations, disrupting occupational roles and interpersonal relationships. These disruptions, in turn, can erode social support networks—an important buffer against affective relapse—and amplify the sense of helplessness or hopelessness experienced by the patient.

From a treatment perspective, clinicians are often faced with a dilemma: hormonal therapies are among the most effective options for controlling the gynecological symptoms of endometriosis, yet they carry the risk of precipitating psychiatric destabilization in individuals with a pre-existing mood disorder. Without clear interdisciplinary protocols, this risk may remain unrecognized until clinically significant symptoms emerge, at which point the patient's psychiatric stability may already be compromised. This highlights an urgent need for integrated care models, in which gynecologic and psychiatric teams collaboratively assess risk, monitor symptom evolution, and adjust treatment strategies in real time.

The case described herein is emblematic of this gap in practice. It underscores the necessity of moving beyond siloed treatment approaches toward a more holistic, patient-centered paradigm—one that acknowledges the interdependence of hormonal regulation, immune activation, and emotional well-being in women managing the dual burden of bipolar disorder and endometriosis (Dalkner et al., 2021).

Despite these clear mechanistic links, standard treatment protocols for endometriosis seldom address psychiatric risk factors, and psychiatric guidelines rarely integrate considerations of hormonal influence on mood stability. The absence of this bidirectional awareness represents a critical gap in patient care. The present case report seeks to bridge this gap by documenting the clinical course of a woman with bipolar II disorder who experienced marked mood destabilization

following sequential hormonal therapies for stage III endometriosis. By integrating detailed clinical observations with a focused review of the relevant literature, this study aims to elucidate the neuroendocrine and immuno-psychiatric mechanisms underlying this phenomenon, discuss its implications for clinical practice, and propose actionable recommendations for interdisciplinary management in similar cases.

METHOD

This study employed a single-case report design to examine the psychiatric impact of hormonal therapy in a patient with bipolar II disorder and stage III endometriosis. The case was selected due to the clear temporal association between changes in hormonal regimen and clinically significant mood destabilization, despite ongoing mood stabilizer treatment. Clinical data included psychiatric history, gynecologic diagnosis, treatment chronology, laboratory results, and structured mood assessments. The Hamilton Depression Rating Scale (HDRS) was administered at baseline and during follow-up to quantify symptom changes.

To contextualize the case within existing evidence, we conducted a structured literature review in PubMed, Scopus, and Google Scholar covering January 2000 to March 2024. Search terms combined "bipolar disorder," "endometriosis," "hormonal therapy," "estrogen," "progesterone," "mood regulation," and "neurotransmitters." Inclusion criteria were English-language, peer-reviewed human studies addressing hormonal therapy and psychiatric outcomes in women. Studies exclusively involving males, animal models, or non-English publications were excluded (Iatrakis et al., 2023).

After screening titles and abstracts, 34 full-text articles were reviewed in depth. Data synthesis focused on identifying patterns of neuroendocrine changes, inflammatory mechanisms, and clinical outcomes relevant to mood regulation in bipolar disorder. The patient's clinical trajectory was then compared against patterns reported in the literature to elucidate possible mechanisms and derive recommendations for clinical management.

RESULT AND DISCUSSION

Case Summary

A 30-year-old woman with a history of bipolar II disorder, stable on lamotrigine for nearly two years, was diagnosed with stage III endometriosis in August 2023. Following the initiation of hormonal therapy, she experienced recurrent mood destabilization temporally associated with changes in medication regimen. Symptoms included agitation, insomnia, irritability, emotional lability, and increased appetite, despite adherence to mood stabilizers. Hamilton Depression Rating Scale (HDRS) scores rose from 9 (mild) at baseline to 21 (moderate–severe) within three months. Laboratory testing during symptomatic periods revealed elevated estradiol (280 pg/mL) and suppressed luteinizing hormone (LH).

Table 1. Treatment Timeline and Symptom Changes

Date / Period	Hormonal Therapy	Mood Symptoms (Key Features)	HDRS Score	Notes
Aug 2023 (baseline)	–	Euthymia	9	Stable mood on lamotrigine 100 mg/day
Sep 2023	Dienogest 2 mg/day (Visanne)	New onset mood lability, irritability, insomnia	14	First emergence of symptoms post-hormonal initiation
Nov 2023	Norethisterone 10 mg/day (Luteron)	Worsening mood swings, agitation, increased appetite, social withdrawal	18	Psychiatric referral considered
Dec 2023	Ethinylestradiol + Levonorgestrel (Microgynon)	Persistent mood instability, mixed affective features, decreased work functioning	21	Quetiapine 50–100 mg/day added as augmentation
Jan 2024	Same regimen	Symptoms partially improved with antipsychotic augmentation; emotional reactivity persisted	17	Multidisciplinary management initiated

Functional Impact

Mood instability led to reduced occupational functioning, prompting a shift to work-from-home arrangements. Social withdrawal and heightened distress over infertility contributed to decreased quality of life.

This case highlights the clinically significant yet underrecognized interaction between hormonal therapy and mood stability in women with bipolar disorder (Freeman, 2010). The clear temporal relationship between changes in hormonal regimen—particularly synthetic progestins—and the onset or worsening of mixed affective symptoms underscores the importance of integrating psychiatric risk assessment into gynecologic treatment planning. While previous research has described hormonal influences on mood, few studies have systematically examined psychiatric outcomes in women with both bipolar disorder and endometriosis, leaving a gap in evidence-based guidance for clinicians.

Dienogest, a selective progestin widely prescribed for endometriosis, has demonstrated favorable efficacy and safety profiles in large-scale cohort studies (Cho et al., 2020). However, while its gynecological benefits are well-established, psychiatric adverse effects are not routinely assessed in these trials. This gap is clinically significant, as illustrated by the present case, where mood destabilization emerged despite the known tolerability of dienogest in somatic domains

Mechanistically, the patient's symptom trajectory aligns with neuroendocrine models in which estrogen generally enhances serotonergic and dopaminergic activity, while synthetic progestins, such as dienogest and norethisterone, may increase monoamine oxidase activity and reduce neurotransmitter availability (Doucet, 2021; Schiller, Johnson, et al., 2015). Additionally,

inflammatory mediators elevated in endometriosis, including IL-6 and TNF-α, may further disrupt mood regulation via effects on the hypothalamic–pituitary–adrenal (HPA) axis (Miller & Raison, 2016; Sherwani et al., 2024). These combined effects likely contributed to the patient's vulnerability to rapid mood destabilization.

Compared with prior literature, this report provides quantitative evidence (HDRS score progression) and a detailed treatment timeline that directly link specific hormonal agents to mood changes, strengthening causal inference. Importantly, despite ongoing mood stabilizer therapy, the destabilization required antipsychotic augmentation, suggesting that hormonal effects can override pharmacologic mood stabilization in susceptible individuals.

From a clinical standpoint, the case supports several actionable recommendations: (1) conduct pre-treatment psychiatric screening for all women with a history of mood disorders prior to initiating hormonal therapy; (2) implement structured, longitudinal mood monitoring—such as repeated HDRS or MDQ assessments—during and after hormonal regimen changes; (3) prioritize hormonal options with lower systemic psychiatric risk, such as localized progestin delivery via levonorgestrel-releasing intrauterine systems or natural progesterone; and (4) maintain close, bidirectional communication between gynecology and psychiatry teams to enable timely treatment adjustments.

By documenting the psychiatric sequelae of hormonal therapy in bipolar disorder with endometriosis, this case underscores the need for integrated care models that address both reproductive and mental health(G.B.D., 2022). Proactive, interdisciplinary management may mitigate the risk of destabilization and improve quality of life for patients navigating the dual challenges of chronic gynecologic and psychiatric illness.

Beyond mood destabilization, bipolar disorder may involve additional maladaptive coping patterns, such as compulsive sexual behavior, particularly under conditions of affective volatility (Putra & Rahman, 2024). This reflects the broader vulnerability of patients to psychiatric sequelae beyond primary mood symptoms. Moreover, drawing parallels to pharmacological adjustments in bipolar cases with metabolic comorbidities (Dewi & Santoso, 2024), our findings reinforce the imperative to personalize hormonal treatments with careful attention to both somatic and psychiatric outcomes.

By documenting the psychiatric sequelae of hormonal therapy in bipolar disorder with endometriosis, this case underscores the need for integrated care models that address both reproductive and mental health(Dall et al., 2022). Proactive, interdisciplinary management may mitigate the risk of destabilization and improve quality of life for patients navigating the dual challenges of chronic gynecologic and psychiatric illness. Additionally, routine use of patient-reported outcome measures and digital mood diaries could enable earlier detection of affective shifts during hormonal transitions. Embedding these tools into gynecology clinics, with rapid psychiatric consultation pathways and shared notes, may improve response times, reduce emergency visits, and sustain adherence to psychiatric and gynecologic treatments.

Case Comparison with Literature

This case aligns with findings from previous research showing that exogenous hormonal treatments can provoke or intensify mood symptoms in women with pre-existing psychiatric vulnerabilities. For instance, Schiller, Meltzer-Brody, et al. (2015) highlighted the role of reproductive steroids in destabilizing mood, particularly during transitions in hormonal state such as postpartum or perimenstrual phases. Similarly, Kulkarni & Butler (2022) emphasized that women with bipolar disorder may exhibit heightened sensitivity to hormonal shifts, particularly with synthetic progestins. While many clinical trials focus on the somatic efficacy of hormonal therapies for endometriosis, few systematically assess their psychiatric side effects, especially in patients with diagnosed mood disorders. This case contributes to the limited body of evidence supporting the hypothesis that hormone-based gynecologic treatments can trigger affective episodes, even when psychiatric medications are continued. The patient's trajectory—improving under mood stabilizers prior to hormonal therapy, followed by mood destabilization after therapy changes—reflects the need for psychiatric oversight when initiating hormone-modulating drugs in susceptible individual

Neuroendocrine and Immuno-psychiatric Mechanisms

The neuroendocrine and immunological pathways provide an integrated model for understanding the exacerbation of mood symptoms in hormonally sensitive individuals. Estrogen plays a neuroprotective role by enhancing serotonergic transmission, increasing dopamine activity, and modulating GABAergic function, all of which are crucial for affect regulation (Frokjaer, 2020). In contrast, synthetic progestins such as norethisterone may downregulate estrogenic activity and increase monoamine oxidase (MAO) levels, which accelerates the breakdown of serotonin and dopamine, leading to emotional instability (Doucet, 2021). Additionally, neurosteroids derived from progesterone such as allopregnanolone—modulate GABA_A receptors, which in some cases can induce sedation or depression depending on receptor sensitivity (Schmidt, 2021). Beyond hormonal factors, inflammatory markers elevated in endometriosis—such as IL-6 and TNF-α—can disrupt the blood-brain barrier, reduce tryptophan availability for serotonin synthesis, and increase hypothalamic-pituitary-adrenal (HPA) axis reactivity (Miller & Raison, 2016). This convergence of neuroendocrine and immunological dysfunction explains why some patients with bipolar disorder may experience more severe or treatment-resistant mood episodes when subjected to hormonal therapies. These mechanisms reinforce the need for a biologically informed approach in managing comorbid reproductive and psychiatric disorders (Al-Harbi & El-Gendy, 2023).

Pharmacological and Psychiatric Implications

Understanding the pharmacodynamic interaction between hormonal therapy and psychiatric medications is crucial in comorbid cases. Mood stabilizers such as lamotrigine and lithium remain the cornerstone in managing bipolar disorder, but their efficacy can be compromised by hormonal fluctuations that influence neurotransmitter systems (Grande, 2016). In this case, despite the patient's adherence to lamotrigine, mood destabilization occurred following hormonal therapy

adjustments, necessitating augmentation with atypical antipsychotics. Evidence suggests that synthetic progestins may blunt the therapeutic response to SSRIs and mood stabilizers by altering serotonergic tone (Kulkarni & Butler, 2022). Additionally, hormonal therapies may exacerbate metabolic burden and contribute to medication side effects, such as weight gain, fatigue, and sedation, which can further impair adherence. From a psychiatric standpoint, careful monitoring of mood symptoms during hormone transitions—particularly initiation or cessation—is essential. Tools such as the Mood Disorder Questionnaire (MDQ) and Hamilton Depression Rating Scale (HDRS) can aid in tracking subtle affective changes over time. Importantly, psychiatric providers should remain informed about the hormonal agents prescribed and consider dose adjustment or preemptive augmentation when hormonal shifts are expected. This collaborative pharmacological vigilance may help mitigate the destabilizing effects of hormone therapy in vulnerable patients.

Clinical and Multidisciplinary Recommendations

The complexity of hormonal and psychiatric interplay in women with comorbid bipolar disorder and endometriosis underscores the necessity for multidisciplinary collaboration Morotti (2017). Gynecologists, psychiatrists, and primary care providers must jointly develop individualized treatment plans that prioritize both emotional stability and gynecological control. Pre-treatment psychiatric screening should become routine practice when initiating hormone-based therapies in patients with a history of mood disorders. Preference should be given to hormonal regimens with lower psychiatric side effect profiles, such as intrauterine devices with localized progestin delivery or natural progesterone rather than synthetic analogs (Kiesel & Sourouni, 2019). Psychiatrists, in turn, should monitor patients longitudinally using structured mood assessments during periods of hormonal adjustment. Psychoeducation also plays a critical role; patients need to be aware of the potential mood effects of hormonal treatment and encouraged to report early signs of emotional changes. Furthermore, mental health support, such as cognitive behavioral therapy (CBT), mindfulness training, or supportive counseling, can serve as important adjuncts (Sasso et al., 2023). These strategies may enhance resilience and reduce symptom severity in hormonally sensitive periods. Ultimately, clinical protocols and guidelines must evolve to include neuroendocrine considerations, ensuring that treatment decisions are informed by both psychiatric and reproductive health perspectives.

Beyond clinical treatment, social and psychological factors play a substantial role in the management of bipolar disorder in women with chronic gynecologic diseases. Emotional distress due to pelvic pain, infertility concerns, and social stigma related to both mental illness and endometriosis may worsen mood instability (Facchin et al., 2015). Multidisciplinary care should not only include medical interventions, but also encompass psychosocial support such as family counseling and access to peer communities. These resources may reduce isolation and enhance long-term outcomes.

Clinicians must be aware that therapeutic success depends not only on disease suppression, but also on emotional stability. Without psychiatric vigilance, hormonal treatment may inadvertently exacerbate the very distress it aims to alleviate.

Patients with coexisting psychiatric and gynecologic conditions often fall through the gaps in fragmented health systems. (Studd & Nappi, 2020) Improved integration between mental health and reproductive health services would enhance diagnostic accuracy, patient satisfaction, and long-term adherence. Bridging this interdisciplinary gap is essential to promote equitable and holistic care for women facing dual burdens (Facchin et al., 2017).

CONCLUSION

This case demonstrates that hormonal therapy, particularly synthetic progestins, can precipitate clinically significant mood destabilization in women with bipolar disorder, even with ongoing mood stabilizer treatment. Clinicians should conduct thorough pre-treatment psychiatric evaluations and maintain close, structured mood monitoring for all women with bipolar disorder undergoing hormonal therapy. Whenever possible, hormonal regimens with lower psychiatric risk, such as localized progestin delivery or natural progesterone, should be considered. Interdisciplinary coordination between gynecology and psychiatry is essential to enable timely adjustments in either hormonal or psychiatric treatment. Future research should prospectively compare the psychiatric effects of different hormonal regimens in women with mood disorders, integrating standardized mood outcome measures to guide evidence-based treatment decisions.

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