



Case Report

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MOOD SWING INDUCED BY CLOMIPHENE IN WOMAN WITH SECONDARY INFERTILITY AND BIPOLAR REMISSION: A CASE REPORT

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Abstract

Previous studies have found that clomiphene citrate (CC), as an infertility medication, may be a significant independent risk factor for the development of depression and has been associated with increased irritability and mood swing. Psychopathological complaints can occur through the mechanism of the Hypothalamic-Pituitary-Gonadal (HPG) axis. While studies of CC in bipolar patients are still lacking, a few reports linked it to exacerbations of prior psychiatric disorders. A case of an adult female who had 7 years of secondary infertility because of endometriosis and a history of bipolar mixed episode, with almost a year of remission, was reported. After 5 days of oral CC for ovulation induction, there was a rapid mood alteration and insomnia on the seventh day, which led to a hypomanic and depressive episode relapse. A clinical case of a bipolar I disorder patient receiving ovarian stimulation with CC to conceive supported this case report, and the relapse symptoms were mild reactive mood swings with no alteration in sleeping pattern. Ovarian stimulation with CC for bipolar women still needs to be approached with caution. Successful management is greatly influenced by the involvement and collaboration with different specialties. One therapeutic approach could be the prescription of second-generation antipsychotics as mood stabilizers.

Keywords: Infertility, bipolar disorder, irritable mood, clomiphene.

Introduction

Clomiphene citrate (CC), as a selective estrogen receptor modulator, can be used for infertility management in women by inducing ovulation. CC binds to receptors of estrogen in the hypothalamus and/or the pituitary gland, inhibiting the binding of endogenous estrogens. It affects the anterior pituitary gland's production and release of FSH and LH.¹ Following CC administration, LH pulse frequency increases, indicating that CC's primary function is to stimulate the hypothalamus' pulsatile secretion of GnRH. This mechanism triggers follicular development and initiates ovulation.^{2,3}

Serious mental adverse events are considered rare with CC, but previous studies found that the psychological impact of CC may be a significant independent risk factor for the onset of depression, because it significantly changes the serum levels of progesterone and estrogen and has been linked to mood swings and irritability.^{4,5} While studies of CC in bipolar patients are still lacking, it can exacerbate pre-existing psychiatric disorders.⁶ This case report presented a case of an adult woman who got CC for infertility, causing mood swings and relapse of bipolar disorder after a 1-year remission episode.

Case Report

A 33-year-old female who had 7 years of secondary infertility due to endometriosis and a history of bipolar mixed episode, with almost a year of remission, was reported. The patient was given CC 25 mg orally for 7 days. After 5 days, there was a rapid mood alteration, as well as insomnia on the seventh day, which led to a hypomanic and depressive episode relapse. The patient was more talkative, had logorrhea in speech, decreased need for sleep, and had impulsive buying. On the same day, the patient also showed an irritable mood, increased sensitivity, and cried more easily. The patient was assessed with the structured Mini International Neuropsychiatric Interview (MINI) ICD-10 when reconsulted to the psychiatrist, where depressive and hypomanic episodes were established, then diagnosed with mixed episode bipolar relapse. The patient was given Quetiapine 200 mg and Lamotrigine 50 mg as mood stabilizers.

The patient had been diagnosed with bipolar disorder since the end of high school, with predominantly depressive episodes. Initially receiving 10 mg of Aripiprazole during hypomanic episodes, the patient subsequently improved and continued taking it regularly. When the patient worked on the final project for her master's degree, the patient experienced insomnia and mood swings, especially the depressive ones. The psychiatrist then added Quetiapine 200 mg and Lamotrigine 25 mg. Afterward, the Aripiprazole was tapered off until she was only taking Quetiapine and Lamotrigine. After graduating, the patient maintained a relatively stable mood for a year without any symptoms and had a partial remission phase. While the pregnancy program

with CC was initiated, the psychiatric symptoms recurred, and the pregnancy program was postponed until the psychiatric symptoms improved.

Discussion

Clomiphene is the first-line agent for treating infertility by stimulating the secretion of hypothalamic GnRH, then increasing the release of gonadotropins to activate ovarian stimulation.^{1,7} Psychiatric adverse effects related to CC, such as mood swings, have been reported in a few case reports. As a selective estrogen receptor modulator, CC can affect the HPG axis, which causes some potential neuropsychiatric effects, especially in vulnerable patients.⁸ Irritability, mood swings, and feeling down were the most psychological side effects of CC. This study described a female patient who got CC to induce ovulation in case of secondary infertility and also had a prior history of mixed bipolar episode. This treatment caused some symptoms to appear, such as mood swings, irritability, and insomnia.

The first study by Rosson et al.⁶ supported this case report, that patients with a prior history of bipolar disorder are more prone to relapse after CC therapy. While the second study by Das et al.⁹ showed that CC causing mood swing was not only in females, but also in males. Sex hormones have been found to regulate mood and may play an essential role in the pathophysiology of affective disorders such as bipolar disorder.⁴ An earlier study involving 454 women found that 77.8% of those taking CC reported at least one psychological side effect, including irritability and mood swings, while 20.4% had sleep disturbance. Not only because of the CC mechanism, but women undergoing infertility treatment have also already been in a state of distress.¹⁰

Given the potential for significant psychological side effects, it is crucial to monitor any changes in mood or behavior in patients who are taking CC. This is also the pivotal role of primary healthcare services in bridging reproductive and mental health care. Informing the patients about the risks of psychological side effects can help them recognize symptoms early and seek help.⁴ Extra caution is advised for individuals with a history of psychiatric disorders when prescribing CC, because of the risk for exacerbated symptoms. By integrating psychiatric screening, patient education, and multidisciplinary collaboration into routine fertility management, primary healthcare can significantly mitigate the risks of mood disturbances associated with CC, especially in patients with a prior bipolar disorder history. Strengthening their involvement ensures safer, more personalized fertility care and supports mental health resilience throughout treatments.

Conclusion

This case highlights that CC may precipitate a relapse of bipolar disorder even in women who have achieved almost one year of remission. The emergence of rapid mood fluctuations, insomnia, and a mixed hypomanic-

depressive relapse shortly after initiating CC suggests a clinically relevant association between ovarian stimulation and mood destabilization. This report adds to the limited literature on CC use in bipolar patients. Also, it underscores the need for careful psychiatric screening, patient education, and close monitoring when prescribing CC to women with prior mood disorders. Collaborative management between primary care, psychiatry, and gynecology, including timely adjustment or optimization of mood stabilizers such as second-generation antipsychotics, is essential to ensure both reproductive and mental health safety in this vulnerable population.

Ethical Considerations: Informed consent was obtained from the patient.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Larson JK, O'Shaughnessy IM, Hutz RJ. Superovulation and Ovulation Induction. In: *Reference Module in Biomedical Sciences*. Elsevier; 2014. doi:10.1016/B978-0-12-801238-3.00265-8
2. Girase T, Patil J, Tatiya A, Patil D, Patil M. Clomiphene Citrate as Nanomedicine Assistance in Ovulatory Disorders and Its Hyphenated Techniques. In: *IOCN 2023*. MDPI; 2023:6. doi:10.3390/IOCN2023-14505
3. Mbi Feh M, Patel P, Wadhwa R. Clomiphene. StatPearls Publishing [Internet]. Published 2024. Accessed September 25, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK559292/>
4. González-Rodríguez A, Cobo J, Soria V, et al. Women Undergoing Hormonal Treatments for Infertility: A Systematic Review on Psychopathology and Newly Diagnosed Mood and Psychotic Disorders. *Front Psychiatry*. 2020;11. doi:10.3389/fpsyg.2020.00479
5. Doyle M, Carballido A. Infertility and mental health. *Adv Psychiatr Treat*. 2014;20(5):297-303. doi:10.1192/apt.bp.112.010926
6. Rosson S, Salvati B, Toffanin T. Ovarian Stimulation for Infertility in a Woman With Bipolar I Disorder. *Prim Care Companion CNS Disord*. 2020;22(6). doi:10.4088/PCC.20l02599
7. Kovalak EE, Özyürek EŞ, Karabay Akgül Ö, Karacan T. Hormonal changes in consecutive clomiphene citrate stimulation cycles and their effect on pregnancy rates. *J Turkish Soc Obstet Gynecol*. 2022;19(3):221-8. doi:10.4274/tjod.galenos.2022.40607
8. Sinha P, Garg A. Could clomiphene kindle acute manic episode in a male patient? A case report. *Gen Hosp Psychiatry*. 2014;36(5):549.e5-6. doi:10.1016/j.genhosppsych.2014.05.011
9. Das M, Ali A, Kumar KA, Menon V. Mania Precipitated by Oral Clomiphene in an Adult Male: A Case Report. *Indian J Psychol Med*. 2023;45(3):319-20. doi:10.1177/02537176221100967
10. Choi SH, Shapiro H, Robinson GE, et al. Psychological side-effects of clomiphene citrate and human menopausal gonadotrophin. *J Psychosom Obstet Gynecol*. 2005;26(2):93-100. doi:10.1080/01443610400022983