

**Oral Contraceptives and Mood Disorders**

by

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## Abstract

**Background information:** Oral contraceptives are one of the most common types of birth control women use to prevent pregnancy. The most widely prescribed pill form contains estrogen and progesterone. Progesterone helps prevent pregnancy while estrogen controls menstrual bleeding. Today, researchers are investigating whether the use of oral contraceptives will increase the chances of developing a mood disorder such as depression or bipolar disorder. These disorders, though common, affect patients by interfering with their daily activities.

**Principal focus:** Behavioral changes were compared to determine if there is a significant increase in the risk of being diagnosed with a mood disorder (i.e. bipolar disorder and depression) among females 13 years and older who use oral contraceptives as their main form of birth control. This was compared to women who did not use oral contraceptives or other female barrier methods such as an IUD, patch, or ring.

**Methodology:** We systematically reviewed 70 clinical trials from UpToDate, PubMed, and the National Library of Medicine using search terms such as oral contraceptives, birth control pills, mood disorders, bipolar disorder, and depression. Limited searches to studies from 2015 to present, English, human trials, and females older than 13 years old. After further reduction, 20 studies were analyzed. Outcomes were accessed via interview assessments or surveys with clinical scores.

**Results:** While there appears to be some supporting evidence demonstrating a correlation between the usage of oral contraceptives leading to increased risk of mood disorders, there are many outside factors that can also influence mood. Therefore more research is still needed to further understand how oral contraceptives alone without any external influence will affect a person's mood.

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## Introduction

Oral contraception has been around since the 1950s and has given countless generations of women reproductive autonomy and freedom. Simply put, a woman may decide to use oral contraceptives to prevent pregnancy. In a century where women's rights and equality were finally getting the recognition they so rightfully deserved, the autonomy over their own bodies was the next step in their long journey to achieving equality as compared to their male counterparts.<sup>1</sup>

When oral birth control was initially developed, it contained high levels of estrogen and progesterone. At this dose regimen, adverse effects, such as mood swings, weight gain, and constitutional changes, were observed. Over the years, advancements have been made to decrease the amount of steroid hormones, which consequently led to a decrease in the number of negative side effects.<sup>1</sup> There are two different formulated birth control pills— the combination pill, consisting of estrogen and progesterone, and one containing progesterone only. Oral contraception prevents pregnancy in three ways: stopping the release of an egg from the ovary, thinning the lining of the uterus which decreases the probability that the fertilized egg will attach to the uterine wall, or thickening the cervical mucus to prevent sperm penetration into the uterus.<sup>2</sup> Birth control has increasingly become a more common practice among female adolescents. For women aged 15 to 44, approximately 25% use contraception, with the oral pill being their preferred form of birth control.<sup>2</sup> There is a growing concern that being on birth control, specifically oral contraceptive pills, at a young age will lead to the development of mood disorders such as depression, and bipolar disorder later in life.

Depression is a mood disorder characterized by a persistent feeling of sadness that interferes with daily functioning. However, being diagnosed with clinical depression differs from the mood swings and feelings of sadness that may accompany the use of oral birth control.

According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, there are several criteria an individual must meet before being diagnosed with depression, including but not limited to depressed mood nearly every day for at least two weeks and associated symptoms such as feelings of worthlessness, guilt, or suicide that affect work or social life. In a study that looked at over a million women aged 15 to 34, only 2.2% of women developed depression.<sup>3</sup> Other studies have shown a positive correlation between depression and suicide, but other confounding variables may affect the relationship.

Bipolar disorder is a mood disorder involving extreme mood swings from emotional "highs" to "lows" which interfere with daily living activities. Emotional "highs" are considered manic episodes which include feeling energized and/or irritable, and depressive episodes, while "lows" consist of sadness and/or hopelessness. It is not uncommon for birth control users to feel mood-related symptoms such as anxiety and/or depression. Almost half of women who tried oral contraceptives stopped using them within the first month because of the frequent, unpleasant changes in mood.<sup>4</sup> Furthermore, hormonal contraceptives can modify the structure and functionality of neurotransmitters in areas of the brain involved with emotional control.<sup>5</sup> Therefore, it cannot be ruled out that those changes could become permanent and contribute to the development of mood disorders. There is a plausible suspicion that the effects that oral contraceptives have on the brain may increase the risk of being diagnosed with a mood disorder. Other risk factors include genetic predispositions or environmental aspects like trauma or stress that influence the development of a mood disorder.

## Methods

This systematic review utilized clinical trials gathered from the following databases: UpToDate, PubMed, and the National Library of Medicine. UpToDate provides accurate physician-authored clinical decision support resources that are continuously updated. PubMed and the National Library of Medicine were utilized for their vast database of available evidenced-based biomedical literature. Search terms used included oral contraceptives, birth control pills, mood disorders, bipolar disorder, and depression. We limited searches to studies from 2015 to the present. 70 studies were found with the initial search and after filtering through with our inclusion and exclusion criteria, 20 studies were reviewed and analyzed for this research. The Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) protocol was also used to help determine which studies were eligible to be included in the review.

### Inclusion:

- Peer review studies published in English.
- Clinical trials that utilized healthy 13-55-year-old female participants.
- Types of studies included are Quantitative and qualitative studies, cohort studies, randomized controlled trials, validation studies, retrospective studies, prospective cohort studies, meta-analysis, cross-sectional studies, and systemic review.
- Mood disorders included: anxiety, depression, emotional instability, and suicidal attempts/idealations.

### Exclusion:

- Studies that included contraceptives outside of oral such as IM, physical ( IUDs, diaphragms, rings), and implants.
- Studies that involved premenstrual and menstrual mood disorders that did not originate from oral contraceptives.
- Study samples included female individuals <13 years of age.

- Studies with sample sizes of less than 20 participants



## Results

### 1. Correlation Between Mood Disorders & Oral Contraceptives

The relationship between oral contraceptives and mood disorders is a subject of growing concern and scientific inquiry. Oral contraceptives have revolutionized women's reproductive health by providing accessible and reliable means of preventing unwanted pregnancies. However, ongoing research suggests that oral contraceptive use may have a significant impact on women's emotional well-being. While the link between the two is complex and not fully understood, it is important to explore this association as it can have implications for the mental health and quality of life of those who use these medications.

A quantitative, prospective cohort study by Skovlund in 2016 gathered information from the Danish Sex Hormone Register Study from Denmark. Data consisted of observed adolescents and women aged 15 to 34 years of age from January 2000 to December 2013. A total of 1,061,997 women with a mean age of 24.4 years were included in this analysis. Users of progestogen-only pills had a relative risk for the first use of antidepressants and adolescents using combined oral contraceptives had a relative risk of first use of antidepressants. Six months after the start use of hormonal contraceptives, the relative risk of antidepressant use peaked. Additionally, in 2018, there was another study done regarding the relationship between hormonal contraception and suicide attempts/suicide by Skovlund. Nearly half a million women were followed for 8.3 years with a mean age of 21 years. Ultimately, the author found that 6,999 women had a first suicide attempt and 71 suicides were identified. The association between hormonal contraceptive use and a first suicide attempt peaked after 2 months of use. Compared with never-users, users of hormonal contraception 15-33 years of age had a relative risk of 1.97 for a first suicide attempt and 3.08 for suicide.<sup>7</sup>

Another article by Gregory (2018) found that hormonal contraceptive use was higher among those ever diagnosed with depression across all age groups with the majority in the 20-24 age range. Data was acquired via the American College Health Association National College Health Assessment Survey administered from Fall 2008 to Spring 2015 across 370 schools nationwide. The survey included females 34 years old and younger. This article further supports the claim that oral contraceptives may contribute to mental health deterioration and mood disorders.<sup>8</sup>

Smith (2018) aimed to assess the relationship between Progesterone-only contraceptives and potential risk factors for developing depressive symptoms. The study analyzed the Beta-arrestin 1 protein level indicating that the reduction in beta-arrestin 1 protein levels in peripheral blood mononuclear leukocytes significantly correlated with the severity of depressive symptoms in reproductive women. The results showed that the level of Beta-Arrestin 1 protein was significantly lessened in women in the Progesterone-only contraceptives compared to women in the non-contraceptive groups.<sup>9</sup>

According to Jung (2019), data was obtained through the survey done by the Korea National Health and Nutrition Examination Survey (KNHANES). Compared to non-users of OC, the likelihood of committing suicide attempt/ideation was calculated using a multivariable logistic regression among OC users. The results revealed that there is an increased prevalence of suicidal ideation in oral contraception users compared to non-users, and a history of depression can modulate the association. However, they emphasized that the limitation of the study is due to the possible recall biases, longitude evaluation of this relationship is warranted.<sup>10</sup>

In a cross-sectional study conducted in Saudi Arabia from October to November 2021, Albawardi et al. (2022) examined the prevalence of depression among women aged 21 and

above using contraceptive methods, excluding those with a history of depression. 4853 participants received a survey covering various aspects, including demographic information, medical and psychiatric history, and contraception details. Out of the participants, 29% exhibited moderate to severe depression. The study revealed higher rates of depression among women using hormonal contraceptives compared to non-hormonal methods. The findings highlight the association between hormonal contraception use and an increased risk of moderate to severe depression in women.<sup>11</sup>

The study conducted by Anderl (2021) investigated the long-term impact of oral contraceptive (OC) use during adolescence on women's vulnerability to depression. Analyzing data from 1,236 participants in the United States National Health and Nutrition Examination Survey, the researchers compared women who initiated OC use during adolescence with those who never used OCs and those who started using OCs in adulthood. The results revealed a significant association: women who began using OCs during adolescence were more likely to experience major depressive disorder (MDD) in adulthood, even years after their first exposure. This link persisted regardless of current OC use and remained after accounting for potential factors such as age at sexual debut. The findings suggest that adolescence might be a critical period during which OC use could heighten the risk of depression in women, emphasizing the importance of understanding the long-term psychological consequences of hormonal contraceptives.<sup>12</sup>

In this population-based cohort study, Johansson (2023) utilized the data from 264,557 women in the UK Biobank to investigate the relationship between oral contraceptive (OC) use and the risk of depression. The study revealed that the first two years of OC use were associated with a significantly higher rate of depression (1.71 times higher) compared to non-users.

Although the risk lessened after the initial two years, the lifetime risk of depression remained elevated (1.05 times higher) among OC users. Notably, adolescent OC users exhibited a particularly increased risk of depression in later life (1.18 times higher). In contrast, no significant association was found among adult OC users who had previously used OCs. Importantly, the study addressed potential biases, including healthy user bias, and employed sibling analysis to support a causal relationship between OC use and depression risk. These findings underline the need for careful consideration of OC use, especially during adolescence, and advocate for personalized risk assessments by healthcare providers and patients.<sup>13</sup>

## **2. No Correlation Between Oral Contraceptives And Mood Disorders**

Throughout our research, we found numerous studies that found a correlation between oral contraceptives and mood disorders. However, for as many studies that found a correlation, we found just as many studies that did not have a connection. The fact that we had roughly an equal amount of research articles that did and did not find a positive association between mood disorders and oral contraceptives will play a huge role in our discussion and conclusion, but that will be discussed later.

A study conducted by Cheslack-Postava (2015) examined the association between oral contraceptive use and major depressive disorder (MDD), panic disorder (PD), and generalized anxiety (GAD) in 20-39-year-old healthy women. The results showed that women who currently used oral contraceptives did not experience MDD, PD, or GAD as much as former oral contraceptive users. Furthermore, after adjusting for confounding variables, women who used oral contraceptives displayed a lower likelihood of developing all 3 disorders, with PD having the lowest threshold. In conclusion, hormonal contraceptives were shown to benefit each individual's mental health and decrease the prevalence of these mood disorders. However, there

were confounding variables such as varying types of oral contraceptives and participants discontinuing the study. In order for the results to be conclusive, the researchers noted that a prospective longitudinal study is necessary.<sup>14</sup>

Lundin (2017) performed a double-blind, placebo-controlled trial with 84 women in the experimental group and 94 women in the placebo group. Women were randomly given either a placebo or a combined oral contraceptive, and then assigned to assess their Daily Record of the Severity of Problems (DRSP). The results were analyzed quantitatively and statistically via Mann-Whitney U/Chi-square tests, and the results were somewhat contradictory. There was an increase in anxiety and irritability but a decrease in depression. A subsequent analysis of the data resulted in discovering that overall mood “deterioration” was relatively similar between the experimental (24.1%) and placebo group (17.0%).<sup>15</sup>

Another randomized and double-blind, placebo-controlled trial performed by Zethraeus (2017) selected 332 healthy women between the ages of 18-35 to either take a combined oral contraceptive or a placebo for 3 months of treatment. Data was collected in the form of answers to these two surveys: Psychological General Well-Being Index (PGWBI) and Beck Depression Inventory (BDI). The results of the surveys were then statically analyzed by independent sample t-tests. The PGWBI had various elements such as mental health perception, vitality, and self-control (Zethraeus et al., 2017). The experimental oral contraceptive group found a statistically significant decrease in general well-being but found no statistically significant difference when it came to depressive symptoms.<sup>16</sup>

McKetta & Keyes (2019) conducted a quantitative study that aimed to determine if oral contraceptive pills (OCP) would increase a patient’s risk of developing major depressive disorder or cause depressive episodes. All participants were female adolescent OCP users with no history

of pregnancy and were examined by using validated, structured interview assessments. The results from this study concluded that there was no correlation between OCP use and major depressive disorder or depressive episodes. Some limitations within this study included inaccurate estimation of depression onset. Because most mood disorders develop between the ages of 18 to 43, we are not certain whether or not depressive episodes will occur as time progresses with the use of OCPs.<sup>17</sup>

A placebo-controlled randomized trial was performed by Scheuringer (2020) which focused on measuring changes in an individual's mood when using combined oral contraceptives (COC). The study consisted of 69 women, all of whom were randomized to have either a 1.5 mg estradiol and 2.5 mg norgestrel acetate or a placebo pill. The results yielded no correlation between COCs and depressive symptoms as COCs did not evoke any differences in emotional interference during the experiment. One major limitation of this study was the small sample size of 69 participants, which could potentially skew the results.<sup>18</sup>

A registered-based cohort study by Lundin (2022) aimed to determine the relationship between combined oral contraceptive (COC) use and increased risk of depression. All 739 participants were 15 to 25-year-old healthy women, currently prescribed hormonal contraceptives, and without a history of antidepressant use. The results from this study showed that oral progestogen-only products have no lower or increased risk of developing depression through hormonal contraceptive use. However, hormonal contraceptive variants that showed an increased risk of developing depression included progesterone-only pills, vaginal rings, implants, and IUDs.<sup>19</sup>

A prospective qualitative and quantitative study was performed by Morssinkhof (2021) which aimed to analyze the likelihood of experiencing depressive or insomnia symptoms during

oral contraceptive (OC) use in healthy premenopausal women. In addition to this assessment, a second objective was to evaluate whether or not having a history of major depressive disorder (MDD) and dysthymia would moderate the association between OC use and depressive or insomnia symptoms. Data from the Netherlands Study on Depression and Anxiety (NESDA) was extracted within a 9-year span by having all 2,981 premenopausal women self-report their symptomatic experiences through diagnostic interviews and questionnaires. The results from this study showed that OC use was not associated with severe depressive or insomnia symptoms, nor with having a history of MDD or dysthymia. Although there were some limitations within this study, such as lifestyle factors, they were addressed within the NESDA.<sup>20</sup>

### **Discussion**

In this systematic review of 15 studies, we explored whether there is a significant increase in the risk of being diagnosed with a mood disorder among females older than 13 years old who use oral contraceptives as their main form of birth control compared to those who did not. We evaluated evidence from 11,947,147 participants that overall showed a weak, positive correlation between hormonal birth control use and increased incidence of diagnosed mood disorders. Out of the 15 studies analyzed, 6 studies showed a positive correlation between oral hormonal birth control and mood disorders defined as depression, anxiety, bipolar disorder, and suicidal ideation/attempts. In contrast, 5 studies found no correlation between hormonal oral birth control use and increased diagnoses of mental health, while 2 of the studies showed mixed results. Each of these studies helps to identify important factors that should be considered when treating women with hormonal birth control and offers other variables that warrant further study.

Studies performed by Skovlund (2018) and Gregory (2018) identified adolescents to be at an increased risk of attempting suicide than other oral hormonal birth control users.<sup>7</sup> Possibly

related to the young age at which many females start oral hormonal birth control, studies performed by Jung 2019 and Johansson 2023 showed evidence of increased mood disorders and suicide attempts within the early time periods of initiating OCP use, which they found to decrease with prolonged use of the birth control.<sup>10, 13</sup> However, Anderl's 2022 study indicates an association in adolescents diagnosed with MDD taking hormonal OCP for up to 6 years after initiating the HOCP.<sup>12</sup> In regards to potential differences among birth control methods and the incidence of mood disorders like depression, Skovlund (2018) evaluated that the patch, vaginal rings, and progesterone-only pills had a higher increase of suicidal ideation, which should prompt further studies into the increase of mood disorders with the forms of birth control that weren't included in this study.<sup>7</sup> In all of these studies, it is determined that there is an increase in mood disorders with the use of oral hormonal birth control. This reminds healthcare providers to be especially vigilant in screening for and treating mental health disorders among women taking hormonal birth control. Part of the duty of healthcare providers is to adequately explain the risks and benefits to patients prior to initiation of a treatment. These studies depict how essential it is to include more education about the risk of mood disorders for women choosing their method of contraception.

The difference in the amount of time a female takes hormonal birth control and changes in risk asks the question: what is the mechanism that increases the incidence of mood disorders? Studies have pondered whether this is a transient change, supported by the increased incidence in the first 12 months, but others may suggest a persistent chemical change. Smith (2018) offers a scientific explanation for the increase in depressive disorders in women using HOCP which supports the persistence of increased prevalence of mood disorders among female HOCP users. Smith studied the mechanism of beta-AR1 protein levels, a biomarker strongly associated with



depression in other studies, and found that women using HOCP had lower protein levels, which significantly correlated with depressive symptoms. However, a significant limitation of this study is the small sample size of 29 women. This could provide an important area of study going forward, as it could be relevant to the millions of women using hormonal birth control worldwide.<sup>9</sup> The studies performed by Cheslack-Postava (2015) and Lundin (2017) displayed inconclusive findings from their methods, which separated anxiety, irritability, depression, and other mood disorders while evaluating the correlation with hormonal birth control. This also supports the necessity of further research into each mood disorder with possible analysis of specific mechanisms to determine the role that birth control might play in increasing the risk for the mood disorder.<sup>14,15</sup>

There are various limitations to the studies included, and discrepancies with the application of the findings to healthcare in the United States. For example, studies included in this meta-analysis were conducted in Saudi Arabia, Korea, the United Kingdom, and Denmark, which have different social norms and different healthcare systems than the United States. The attitudes and approach may vary depending on the societal views regarding birth control measures, mental health, and the methods providers use to address these topics. Additionally, the ability of patients in the United States to access care for birth control methods and mental health will vary from these other countries due to the organization of their healthcare systems.

Furthermore, many factors contribute to the incidence of mood disorders that may confound the correlation with oral hormonal birth control use. For example, historically, oral contraceptive pills are cheaper than other forms of birth control, which could increase the participation of women from socially disadvantaged groups in these studies. Another consideration is that there may be a false association of hormonal birth control use with mood

disorders, as it is easier for those already seeing providers for this service to have their mood disorders more readily screened and evaluated. Due to the widespread use of hormonal contraceptives among a broad spectrum of women across the world, it is important to properly acknowledge and address the potential side effects of this method. It is equally important, however, to have significant evidence before making claims that could jeopardize the use and acceptance of these revolutionary drugs. Therefore, the weakly positive association between hormonal oral birth control and diagnosed mood disorders should promote further consideration and actions of healthcare providers, but should not undermine the importance of their role.

### **Conclusion**

It remains unclear if contraceptive use increases the risk of a woman developing a mood disorder. In this review of twenty peer-reviewed research articles, there appears to be a slightly positive correlation between oral contraceptive use and mood disorder prevalence. While the list of side effects of using oral contraceptives remains a long one, it is questionable if developing a mood disorder is one of them. More research and longitudinal studies need to be conducted looking at the relationship between oral contraceptives and mood disorders, specifically anxiety, depression, and bipolar disorder.

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