Medical Science

Oral contraception use and depression: Review

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DISCOVERY SCIENTIFIC SOCIETY

ABSTRACT

Background: Oral contraceptive pills are an effective and widely used method of contraception that offers various health benefits; however, their potential impact on mood and other depressive symptoms remains contentious. This review aims to evaluate the effects of COC use on depression by analyzing recent randomized controlled trials (RCTs). *Method*: A systematic search was conducted across PubMed and Google Scholar databases for RCTs published from 2010 to 2024. The review concentrated on studies that assessed the impact of COCs on depressive symptoms using standardized measurement tools. Following rigorous screening, five studies were included in the analysis. *Results*: The review concludes that the relationship between oral contraception and depressive symptoms is ambiguous. While some studies confirmed an association between COCs and mood deterioration, particularly in women with a history of mood-related side effects, others found no significant impact or even potential mood improvement in specific populations, such as those with premenstrual dysphoric disorder (PMDD). There are also indications that oral contraceptive use in adolescents might lead to an increased risk of depression in adulthood. *Conclusion*: The relationship between COC use and mood is complex and influenced by individual factors. Healthcare providers should engage in comprehensive conversations with patients regarding the potential psychological side effects of COCs to ensure informed and personalized contraceptive care.

Keywords: Depression, oral contraception, combined oral contraceptives

1. INTRODUCTION

(Oral contraceptive pills (OCPs)) are widely considered one of the most effective methods of contraception. It is estimated that within a year of using OCPs, unplanned pregnancy will affect 7 out of 100 sexually active women. However, if used as recommended and no mistakes are made, the estimates will be less than 1 in 100 (3 in 1,000), equivalent to a Pearl index of 0.03. These values apply to both (progestin-only pills (POPs)) and (combined contraceptive pills (COCs)], containing progestins and estrogen (WHO/SRH and CCP, 2022). Oral

contraceptive pills are also one of the most widely used methods of contraception. According to the United Nations Department of Economic and Social Affairs, Population Division, (2022), globally, 966 million women of reproductive age (15-49 years) are using some method of contraception, of which 15.7% (about 150 million women) use OCPs.

Thus, the oral contraceptive pill is the fourth most common (after female sterilization, male condoms, and intrauterine devices) method of hormonal contraception used worldwide. As for Europe, the OCP is the most common method of contraception, used by 19.1% of women of reproductive age. It is also the most commonly used method of contraception in the U.S. - about 25% of women aged 15-44 refer to OCP as their method of choice (Cooper and Patel, 2024). In addition to preventing pregnancy, oral contraception pills provide other health benefits, including protection against endometrial Collaborative Group on Epidemiological Studies on Endometrial Cancer, (2015), ovarian Bosetti et al., (2002), and colorectal cancer (Bosetti et al., 2009).

About 14% of U.S. women use them for non-contraceptive reasons, such as addressing menstrual-related disorders like menstrual pain or irregular menstruation (Cooper and Patel, 2024). They have been proven to reduce symptoms of hirsutism and the severity of acne (Amiri et al., 2018; Arowojolu et al., 2012). OCPs are also one of the most effective methods of reducing the severity of pain associated with endometriosis (Samy et al., 2021). However, it is worth remembering that the use of COCs is associated with a higher risk of thromboembolism (Dragoman et al., 2018). OCP use may also be linked to an elevated risk of developing cervical cancer (Asthana et al., 2020). Despite its many benefits, OCPs also involve the risk of negative side effects. According to a clinical trial by Chen et al., (2022), most participants (52.3%) reported one or more side effects associated with COC use.

Among the most commonly reported were bleeding complaints, breast pain or tenderness, acne, mood disturbance, headache, dysmenorrhea, and increased weight. A prospective evaluation of frequency and reasons for oral contraceptive discontinuation by Rosenberg et al., (1998) indicates that 46% of women who have decided to stop taking OCP have done so because of the negative side effects. The side effects most frequently reported were bleeding irregularities, followed by nausea, weight gain, mood changes, breast tenderness, and headaches. As noted, mood changes are one of the more frequently reported negative effects of OCPs.

On the other hand, OCs containing drospirenone are considered a second-line treatment for (premenstrual dysphoric disorder (PMDD)) Lanza-di-Scalea and Pearlstein, (2019) - a psychiatric diagnosis that is associated with depressed mood and irritability related to menstrual cycles (World Health Organization, 2022). The results of cohort or cross-sectional studies are inconsistent and indicate both the presence Johansson et al., (2023), Skovlund et al., (2016) and absence Lundin et al., (2022), Toffol et al., (2012) of an association between the use of oral contraceptives and depressive symptoms. However, few randomized controlled trials have been conducted on the subject. This paper aims to evaluate RCTs on the effects of COCs on mood.

2. METHOD

A systematic search using the following databases was conducted to provide a thorough literature review: Elsevier, PubMed, Cochrane Library, and Google Scholar. The search included articles published from 2010 to 2024. Keywords used in the search were ("oral contraception", "combined oral contraceptives", "depression", "depressive symptoms", and "mood changes"), combined with Boolean operators ("AND", "OR") to refine the results. Studies were chosen according to predefined inclusion and exclusion criteria. The inclusion criteria were as follows: Studies based on standardized and validated tools for measuring depressive symptoms, studies investigating the impact of COCs on depressive symptoms, study populations consisting of women of reproductive age (18-45 years), articles published in English, and articles published after 2010, randomized control trials.

The exclusion criteria for the studies were: Studies that did not use a placebo control, non-randomized studies, cohort studies, cross-sectional studies, case reports, and review articles; studies focusing only on other types of hormonal contraceptives (e.g., progestin-only pills, hormonal intrauterine devices) and studies not reporting specific outcomes related to depressive symptoms. Following thorough analysis, five articles were selected that offered the most valuable insights into the association between COC use and depressive symptoms. A flow diagram was used to record the study selection procedure (Figure 1).

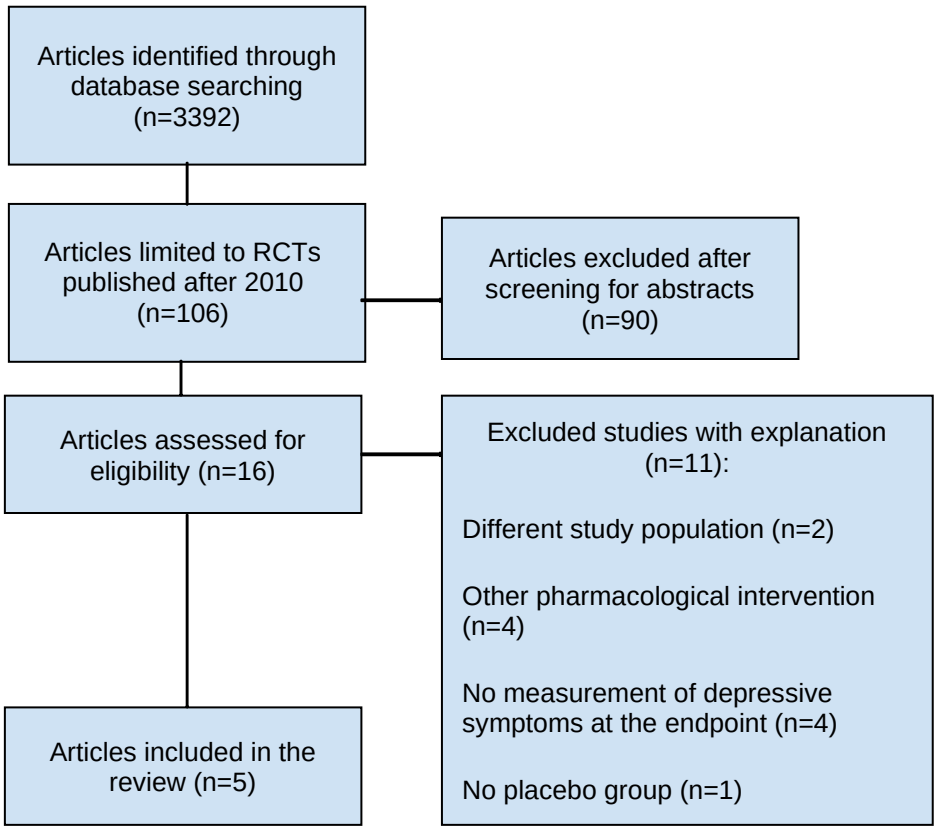

Figure 1 Study selection process for literature review of COC use and depression.

3. RESULTS

A total of 1218 articles were initially gathered from various databases. After applying initial inclusion criteria (RCTs published after 2010), 106 articles were screened based on their titles and abstracts, resulting in 16 full-text articles being assessed for eligibility. Ultimately, five studies were included in the review (Figure 1). Only studies that used standardized and validated tools for measuring depressive symptoms, such as the (Montgomery and Åsberg Depression Rating Scale (MADRS)) or the (Beck Depression Inventory (BDI)) were included.

Symptoms of a depressive episode do not only include lowered mood but also diminished interest or pleasure in activities, difficulty concentrating, beliefs of low self-worth, hopelessness about the future, recurrent thoughts of death or evidence of attempted suicide, disrupted or excessive sleep, change in appetite, fatigue and psychomotor retardation or agitation (World Health Organization, 2022). The above scales consider these symptoms (Montgomery and Asberg, 1979; Beck et al., 1961). Some studies have also used the (Daily Record of Severity of Problems (DRSP)) scale, which is used to aid in the diagnosis and evaluation of DSM-IV Premenstrual Dysphoric Disorder (PMDD) and considers changes in mood, such as feeling depressed or mood swings (Endicott et al., 2006). The findings of the analyzed studies are summarized in a table (Table 1).

The main goal of the study conducted by Scheuringer et al., (2020) was to determine whether the use of combined oral contraception influences cognitive-emotional processing or depressive symptoms. Somatically healthy women aged 18-35 participated in the study. Women with ongoing or previous mental disorders and women who reported present use of psychotropic drugs were also included. The treatment group received COC of 1.5 mg estradiol and 2.5 mg nomegestrol acetate for three cycles. Depressive symptoms were measured using the MADRS. An emotional verbal Stroop task was used to assess cognitive-emotional processing. There was no interaction between emotional interference to the three-word categories (positive, anxiety, and depressive) and treatment with COC.

There were no statistically significant differences in MADRS scores between the COC and placebo groups, both at baseline or during treatment. Treatment with COC did not predict depressive symptoms at the end of the trial. However, there were some significant predictors of depressive symptoms at the end of the trial, including trait anxiety at baseline and a history of prior adverse mood effects during hormonal contraceptive use. Lundin et al., (2017) examined the relationship between the use of COC and mood changes in different phases of the treatment cycles. The study population consisted of healthy women aged between 18 and 35. For the study population to be representative of general users, ongoing psychiatric disorders, the present use of psychotropic drugs, or previous adverse mood symptoms while using COC were not reasons for exclusion.

The treatment involved using COC consisting of 1.5 mg estradiol and 2.5 mg nomegestrol acetate and lasted three cycles. Mood and depressive symptoms were estimated with MADRS and DRSP. There was no difference in MADRS scores measured during the premenstrual phase between the COC and placebo groups, both at the baseline and the final treatment cycle. There were some women with a new onset of subclinical depression during treatment, but their number didn't differ between the COC and the placebo group. Regarding DRSP scores, COC use was associated with a small increase in mean anxiety, irritability, and mood swings during the intermenstrual phase. On the other hand, it was also associated with a decrease in mean depression levels during the premenstrual phase.

Although the main goal of the study conducted by Petersen et al., (2021) was to determine whether COC use affects (magnetic resonance imaging (MRI)) measures of prefrontal cortical thickness, it also included measuring mood-related symptoms using DRSP and BDI. Researchers hypothesized that these possible prefrontal cortical brain structure changes may influence mood regulation. Participants were healthy women aged between 18 and 35 who had reported previous mood deterioration while using COC. Women who were experiencing a current psychiatric disorder were excluded from the study. The treatment included using 0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel pill for one cycle (21 days) and was followed by a washout period comprised of one complete menstrual cycle. COC use was associated with an increased total score of self-reported symptoms on the DRSP compared to placebo.

The statistically significant increase applied to the following items of DRSP: "feeling overwhelmed", "physical symptoms", "reduced productivity", and "social avoidance". There was no significant change regarding items "feeling depressed" and "mood swings". However, COC significantly increased symptoms of depression assessed with the BDI. COC use reduced prefrontal cortical thickness, but cortical thickness and mood symptoms were unrelated. Zethraeus et al., (2017) examined the influence of COC on general well-being, assessed with the (Psychological General Well-Being Index (PGWBI)). Depressed mood is one of the PGWBI's dimensions. To measure depressive symptoms, researchers also used the BDI.

The study population consisted of healthy women aged between 18 and 35. There is no information on whether the participants had previously experienced mood-related side effects of COC. The treatment consisted of a combined monophasic pill containing 0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel and lasted three months. There was a statistically significant difference in the total score of PGWBI between the treatment and the placebo groups. The statistically significant negative impact applied to dimensions of PGWBI like "positive well-being", "self-control", and "vitality". However, there was no significant effect in the dimension of "depressed mood". There was also no statistically significant negative effect for depressive symptoms as assessed by the BDI.

The study by Gingnell et al., (2013) focused on mood-related side effects and changes in brain reactivity related to the use of COC among women with a history of mood deterioration during COC treatment. Participants were healthy women aged between 18 and 45 who reported previous side effects of COC, including depressed mood, anxiety, mood swings, irritability, or decreased interest in usual activities. Women with an ongoing psychiatric disorder or with a history of use of psychotropic drugs within two months before recruitment were excluded from the study. Participants were treated with a COC containing 0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel for one treatment cycle (21 days). The (Cyclicity Diagnoser (CD)) scale assessed mood and physical symptoms. Negative mood parameters of the CD scale include depression, interest in usual activities, fatigue, irritability, being anxious or worried, mood swings, sense of being out of control, difficulties in concentrating, and disordered sleep.

Depressive symptoms were also measured using the MADRS. Functional magnetic resonance imaging (fMRI)) was performed to assess brain activity. Changes in emotional brain reactivity, such as lower activity in the left insula, accompanied COC use. Regarding mood deterioration, the use of COC was associated with higher scores of depressed mood, mood swings, and fatigue assessed by the CD scale in comparison with placebo users. COC users also increased their scores of depressed mood, mood swings, and fatigue in comparison to the pretreatment cycle. Such a relationship was not observed among placebo users. Depression level, measured by

MADRS-s, significantly increased among COC users during the last week of the treatment cycle compared to their pretreatment ratings.

Table 1 RCTs investigating the impact of COC on mood

Study	Participants	COC composition	Mood Measurement Tools	Results
Scheuringer et al., (2020)	Healthy women aged 18-35, including women with current or past mental disorders or use of psychotropic drugs	1.5 mg estradiol and 2.5 mg nomegestrol acetate	MADRS	Treatment with COC did not predict depressive symptoms at the end of the trial. Predictors of depressive symptoms: Trait anxiety at baseline and history of prior adverse mood effects during hormonal contraceptive use.
Lundin et al., (2017)	Healthy women aged 18-35, including women with current psychiatric disorders, use of psychotropic drugs, or past mood issues with COC	1.5 mg estradiol and 2.5 mg nomegestrol acetate	MADRS, DRSP	No difference in MADRS scores between the COC and placebo groups. COC use was associated with a small increase in irritability, anxiety, and mood swings during the intermenstrual phase but a decrease in depression during the premenstrual phase.
Petersen et al., (2021)	Healthy women aged 18-35 with previous mood deterioration on COCs, excluding women with current psychiatric disorders	0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel	DRSP, BDI	Significant increase in BDI scores in the COC group. COC use increased total DRSP scores for feeling overwhelmed, physical

				symptoms, reduced productivity, and social avoidance. There were no changes in scores for feeling depressed and mood swings.
Zethraeus et al., (2017)	Healthy women aged 18-35. There was no information on whether the participants had previously experienced mood-related side effects of COC	0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel	PGWBI, BDI	COC had a significant negative impact on the PGWBI total score but no significant effect on the "depressed mood" dimension. No significant effect on BDI scores.
Gingnell et al., (2013)	Healthy women aged 18-45 with previous mood deterioration on COCs, excluding women with current psychiatric disorders or use of psychotropic drugs	0.30 μg ethinyl estradiol and 0.15 mg levonorgestrel	CD scale, MADRS	Higher scores of depressed mood, mood swings, and fatigue on the CD scale in the COC group compared to placebo. Significant increase in MADRS scores during the last week of the treatment cycle among COC users.

4. DISCUSSION

As shown, the results of RCTs on the relationship between COC use and depression are inconclusive. Some show that the use of COCs may be associated with mood deterioration Petersen et al., (2021), Gingnell et al., (2013), others that it may result in mood improvement Lundin et al., (2017), and others indicate that there is no relationship (Scheuringer et al., 2020; Zethraeus et al., 2017). It is worth noting, however, that the two studies showing an association between COC use and mood deterioration were conducted only among women who had reported previous mood-related side effects while using COCs. It is consistent with the conclusion of Scheuringer et al., (2020) that the history of prior adverse mood effects during hormonal contraceptive use was a predictor of depressive symptoms at the end of the trial.

Thus, it appears that the worsening of mood after using COCs mainly affects women who show some kind of susceptibility. Among the populations studied, women with current or past mental disorders were present, which may have affected the results. The role of a prior diagnosis of depression as a risk factor for COC-related mood changes remains inconclusive. While some studies suggest that a history of depression does not necessarily increase the risk of mood deterioration with COC use Morssinkhof et al., (2021), others

identify it as a significant predictor (Joffe et al., 2003; Lundin et al., 2021). Interestingly, women with premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) may experience mood improvement with COC use.

Studies indicated that COCs, particularly those containing drospirenone, could alleviate premenstrual depressive symptoms (Nyberg, 2013; Freeman et al., 2001). It suggests that PMS or PMDD should not be considered a contraindication for COC use; instead, these conditions might benefit from specific COC formulations. One of the factors that contribute to increased vulnerability to depression associated with the use of COCs may be adolescent age. Research indicates that initiating COC use during that period may be related to a higher risk of depression in adulthood (Anderl et al., 2020; Anderl et al., 2022; Johansson et al., 2023). There are hypotheses that specific vulnerability to depression among some young women can be catalyzed by cyclic fluctuations of gonadal steroids (Joffe and Cohen, 1998).

Gordon et al., (2015) propose an explanatory model according to which increased vulnerability to depression may be caused by a failure of the GABAA receptor in the face of shifting levels of neurosteroids, resulting in hypothalamic-pituitary-adrenal axis dysfunction. Some researchers suggest that adolescence may be a sensitive period during which the use of oral contraception could cause long-lasting changes in the brain, resulting in an increased risk of depression (Anderl et al., 2020). Therefore, careful consideration and thorough counseling are essential when prescribing COCs to young women. The inconsistency of the results underscores the importance of individualized patient assessment and monitoring during COC use, especially for those with a mental health history. Despite the widespread use of OCPs, there is a gap in healthcare providers' communication about the potential psychological side effects of these contraceptives.

Studies suggest that many providers do not adequately address these concerns during contraception counseling (Martell et al., 2023). Healthcare professionals must be well-informed about the current evidence on the psychological effects of OCPs to offer comprehensive and personalized counseling. Addressing patients' concerns can improve adherence and satisfaction with contraceptive choices. Future research should strive to explore the mechanisms that contribute to individual susceptibility to mood changes caused by COC use. Longitudinal studies with diverse populations and advanced neuroimaging techniques could provide deeper insights into how COCs influence mood and brain function over time. Additionally, developing and testing new formulations of COCs that minimize adverse mood effects could enhance the quality of life for many women.

5. CONCLUSION

While COCs are a highly effective and commonly used method of contraception, their potential impact on mood warrants careful consideration. The relationship between COC use and depressive symptoms is not straightforward and appears to depend on individual factors. Healthcare providers must engage in informed discussions with patients about the benefits and risks of COC use, ensuring personalized and supportive contraceptive care.

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Dominika Kabała: Conceptualization, writing- rough preparation, methodology, resources
Michał Bielecki: Conceptualization, writing- rough preparation
Adam Jaskulski: Writing- review and editing, resources
Marcin Głód: Methodology, supervision
Milena Szczepańska: Formal analysis, investigation
Agata Zapałowska: Conceptualization, supervision
Tymon Zatorski: Resources, visualization
Project administration: Dominika Kabała
All authors read and approved the final manuscript.

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The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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