**Impacts of oral contraceptive use on depressive and anxious symptoms: an integrative review**

**ABSTRACT**

**Aims:** This study aims to integratively review the psychological impacts of oral contraceptive (OC) use, focusing on depressive and anxious symptoms. It analyzes the role of age, OC formulation, mental health history, and genetic predisposition, and highlights the importance of personalized prescription to minimize adverse outcomes.

**Study Design:** Integrative literature review.

**Place and Duration of Study:** Databases searched (PubMed, SciELO, MEDLINE, LILACS, BVS) on November 20, 2024, including studies from 2014 to 2024.

**Methodology:** PRISMA guidelines were followed. Boolean descriptors included "oral contraceptives," "depression," "anxiety," and related terms. Inclusion criteria comprised primary studies (quantitative, qualitative, mixed-methods) evaluating the relationship between OC use and emotional symptoms in women. Reviews and studies lacking focus on mental health outcomes were excluded.

**Results:** Adolescents showed increased vulnerability to depressive and anxious symptoms associated with OC use, especially with progestin-only formulations. Combined OCs (estrogen + progestin) were more often linked to emotional stability, particularly in adults without psychiatric histories. Monophasic pills had fewer mood effects than multiphasic ones. Genetic predisposition and a history of mental disorders increased emotional risks. Some subgroups experienced reduced emotional variability with OC use.

**Conclusion:** Emotional effects of OCs vary with age, type of formulation, and mental health history. Personalized contraceptive choices and close clinical monitoring are essential, especially for adolescents and women with psychiatric vulnerability. Longitudinal studies are needed to clarify long-term impacts and biological mechanisms.

1. **INTRODUCTION**

Oral contraceptives (OCs) have been widely utilized since their introduction in the 1960s, primarily as a means of family planning. Over the decades, research has expanded to explore their broader physiological and psychological effects. Early observations suggested a potential link between hormonal contraceptives and mood changes, yet the mechanisms underlying these effects remained unclear. More recent studies have aimed to elucidate how synthetic hormones influence emotional well-being, particularly through their impact on the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmission (1-5).

The HPA axis, a central component of the body's stress response system, plays a crucial role in regulating cortisol levels, which influence mood and emotional stability. Oral contraceptives, particularly those containing progestin, have been implicated in modulating HPA activity, potentially leading to alterations in stress reactivity. Additionally, neurotransmitter systems, such as serotonin and gamma-aminobutyric acid (GABA), are affected by hormonal contraceptive use, contributing to observed changes in depressive and anxious symptoms (6, 7,20).

Historically, the relationship between oral contraceptives and mental health has been debated, with conflicting findings arising from epidemiological and clinical studies. Initial reports highlighted mood disturbances in some OC users, while later research indicated that combined estrogen-progestin formulations might have mood-stabilizing effects in certain populations. These inconsistencies underscore the complexity of hormonal influences on brain function and emphasize the need for individualized approaches to OC prescription (3, 6).

The present review seeks to synthesize the available literature on the psychological effects of oral contraceptive use, identifying key factors such as age, contraceptive formulation, and mental health history that contribute to varied responses. By examining both biological mechanisms and clinical findings, this study aims to provide a comprehensive understanding of the impact of hormonal contraceptives on mood and anxiety disorders, with implications for personalized healthcare strategies (8, 9).

1. **MATERIAL AND METHODS**

**Inclusion and Exclusion Criteria**

This integrative review includes quantitative, qualitative, or mixed-method studies investigating the impacts of oral contraceptives (OCs) on depressive and anxious symptoms. Eligible articles were published between 2014 and 2024, available in Portuguese, English, and Spanish, and indexed in the SCIELO, PubMed, MEDLINE, LILACS, and BVS databases. The target population included women using OCs, regardless of age or social context, as long as the studies explicitly addressed the relationship between OC use and mental health symptoms such as depression, anxiety, insomnia, or mood changes.

Excluded studies were those that did not explore the connection between OC use and mental health, including those focused solely on physiological, metabolic effects, or contraceptive efficacy. Systematic reviews, meta-analyses, and opinion articles were also excluded to prioritize primary and original studies. Additionally, duplicate articles and studies with severe methodological limitations, such as a lack of clarity in methods or insufficient primary data, were eliminated.

**Publication Bias**

Publication bias was considered, as studies with positive findings are more likely to be published than those with neutral or negative results. This can influence conclusions by overestimating certain effects. To mitigate this bias, the search strategy included multiple databases and diverse methodological approaches. The integrative review approach allows for the synthesis of studies with different designs, including clinical trials, observational studies, and systematic reviews, enabling a comprehensive evaluation of biological, social, and emotional factors influencing the psychological effects of OCs. Additionally, this method helps identify research gaps and guides future investigations, contributing to evidence-based clinical practice.

**Search Strategy**

The literature search was conducted in the PubMed, SciELO, MEDLINE, LILACS, and BVS databases using the following Boolean operators and keywords:

Chart 1. Boolean operators and keywords

|  |  |
| --- | --- |
| Database | Boolean Operators and Keywords |
| PubMed | "oral contraceptives" AND "depression" AND "anxiety" |
| SciELO | "contraceptives" OR "oral contraceptives" AND "emotional symptoms" |
| MEDLINE | "hormonal contraceptives" AND "mental health" |
| LILACS | "oral contraceptives" AND "psychological effects" |
| BVS | "contraceptive use" AND "mental health symptoms" |

Source: Authors (2025).

The search was conducted on November 20, 2024, covering studies published from 2014 to 2024. The use of Boolean operators ensured the inclusion of studies addressing specific psychological impacts of OCs while allowing a broader scope for general emotional effects. This methodological approach enhances the transparency and reproducibility of the review.

**Study Selection**

The study selection process followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was structured into four stages: identification, screening, eligibility, and inclusion.

Identification: a comprehensive search was conducted in the selected databases using the Boolean combinations mentioned. A total of 123 studies were initially identified.

Screening: duplicate studies (24) were removed, leaving 99 articles. Titles and abstracts were reviewed, excluding those not directly addressing OC use and emotional symptoms, reducing the count to 53 articles.

Eligibility: full texts of the remaining 53 studies were analyzed, resulting in the exclusion of 34 articles due to systematic review/meta-analysis nature, low methodological quality, or focus on unrelated outcomes such as metabolic effects. This left 19 eligible studies.

Inclusion: the final 19 selected studies encompassed diverse methodological approaches (quantitative, qualitative, and mixed analyses), ensuring a robust dataset for analysis. A PRISMA flowchart was used to document each stage, enhancing transparency and reproducibility.

**Data Analysis**

The data from the included studies were analyzed using a combination of narrative synthesis and thematic categorization. Initially, extracted information was organized into an analytical matrix containing study type, evaluated population, type of OC investigated, analysis methods, and key findings on depressive and anxious symptoms. This approach facilitated pattern recognition and gap identification across the studies.

Thematic analysis categorized results into key areas:

* The impact of OCs on depressive symptoms;
* The relationship between OCs and anxiety symptoms;
* Differences between combined and progestin-only contraceptives;
* Moderating factors such as age, psychiatric history, and genetic predisposition

Narrative synthesis was used to integrate findings, comparing different contraceptive formulations, evaluated populations, and specific contexts. This enabled a broad interpretation of the results, identifying clinical and research implications. The methodological combination ensured a structured and thorough analysis, respecting the heterogeneity of included studies and providing a solid foundation for interpreting and applying the results.

1. **RESULTS**

**Chart 2. General Description of Included Studies**

|  |  |
| --- | --- |
| Aspect | Description |
| Number of Articles | 14 studies included. Sample sizes range from small studies (<100 participants) to large epidemiological studies (>800,000 women). |
| Temporal Distribution | Published between 2015 and 2023, with an increase in recent years (2017–2023). |
| Countries of Origin | Sweden, USA, Netherlands, Germany, and the United Kingdom. Represent high-income countries with diverse populations. |
| Types of OCs Studied | Combined (estrogen + progestin), Progestin-Only, Monophasic, and Multiphasic. |
| Study Designs | Epidemiological studies, Randomized Clinical Trials, Animal Models, Neuroimaging, and Biomarker Studies. |
| Study Focus | General Mental Health, Neurobiological Impacts, Adolescents, Interactions with Psychological Treatments. |
| Key Findings | • Combined OCs were frequently associated with emotional stabilization, while progestin-only formulations were more often linked to adverse mood changes. • Women with a psychiatric history or genetic predisposition to stress showed a higher risk of emotional symptoms. • Adolescents exhibited greater sensitivity to hormonal changes, with prolonged effects on mental health. |

*Source: Authors (2025).*

**OCs and Depressive Symptoms**

Studies on the relationship between oral contraceptive (OC) use and depressive symptoms provide evidence that varies according to factors such as age, mental health history, and type of contraceptive used. Among adolescents, OC use was consistently associated with an increase in depressive symptoms compared to non-users. Data from a prospective study showed that adolescent OC users had a higher prevalence of crying episodes (odds ratio [OR] 1.89; confidence interval [CI] 95%, 1.38–2.58), hypersomnia (OR 1.68; CI 95%, 1.14–2.48), and eating disorders such as binge eating, anorexia, and bulimia nervosa (OR 1.54; CI 95%, 1.13–2.10). These symptoms were not significantly observed in older women, suggesting a specific vulnerability of adolescents to the hormonal impact of OCs (3, 8).

In adult women, particularly those with a history of adverse effects from hormonal contraceptives, OC use was associated with a higher prevalence of depressive symptoms in some studies, though without robust statistical significance. This indicates that susceptibility may be modulated by individual factors such as genetic predisposition and psychiatric history. While OC use may be associated with small mood variations during the treatment cycle, there is no evidence of a significant increase in general depressive symptoms. In one study, a slight worsening of mood during the intermenstrual phase was observed (mean difference: 0.22; CI 95%, 0.07–0.37), but depressive symptoms improved during the premenstrual period (-0.33; CI 95%, -0.62 to -0.05) (2, 4).

Prolonged OC use initiated during adolescence has long-term implications for mental health. A prospective study indicated that adolescents who used OCs had a higher risk of developing major depressive episodes in adulthood (median OR 1.41; minimum OR 1.08; maximum OR 2.18; p<0.001). This association was especially evident in women with no prior history of depressive disorders, suggesting that adolescence may be a sensitive phase for the effects of contraceptive hormones (3, 7, 9).

Additionally, progestin-only contraceptives have been associated with a higher risk of depressive symptoms compared to combined contraceptives. A pilot study found that women using progestin-only contraceptives scored significantly higher on the Hamilton depression scale compared to users of combined contraceptives (p<0.004) (6).

**OCs and Anxious Symptoms**

Among adolescents, OCs have been associated with significant changes in emotional behavior and stress response. A study conducted in an adolescent population found that OC use during this critical developmental phase is related to an attenuated stress response, accompanied by structural and functional changes in brain areas associated with emotional processing and memory. These findings suggest that early exposure to contraceptive hormones may impact neural plasticity in a lasting way. Studies also indicate that women with a prior history of mental disorders are more predisposed to anxiety symptoms induced by OC use. A randomized clinical trial found that women with previous psychiatric disorders or a history of alcohol abuse experienced higher intensity of anxiety symptoms during the use of combined hormonal contraceptives compared to women without such a history (10, 11).

On the other hand, emerging evidence suggests that OCs may have stabilizing effects in certain contexts. A systematic review showed that in healthy women, OC use was associated with reduced emotional variability and a lower prevalence of anxiety symptoms, indicating a potential hormonal regulatory effect on emotional behaviors. Moreover, the type of contraceptive appears to play a crucial role. An experimental study using animal models revealed that OC formulations containing levonorgestrel were associated with an attenuated response to acute stress, while other formulations showed no significant effects on anxious behavior. These findings provide important insights into how different hormonal combinations modulate stress reactivity and anxiety (12, 13).

The relationship between OCs and anxiety symptoms is also influenced by social and psychological contexts. Clinical studies point out that women using hormonal contraceptives demonstrate differences in fear exposure tasks and avoidance behavior, suggesting that OCs may impact the response to non-pharmacological treatment for anxiety disorders. Lastly, a pharmacological investigation highlighted that among adolescents, the use of hormonal contraceptives is related to a higher likelihood of psychotropic medication prescriptions, including anxiolytics, indicating that this population may be particularly sensitive to the psychological effects of hormonal contraceptives (14, 15).

**Conditions Influencing the Relationship Between Oral Contraceptives and Anxiety or Depressive Symptoms**

**Table 1: Age and Developmental Stage**

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| --- | --- | --- |
| **Life Stage** | **Characteristics** | **References** |
| Adolescents and Young Adults | • Higher risk of emotional changes due to brain maturation; • Hormonal interaction may exacerbate stress responses. | 10 |
| Adults and Elderly | • Lower overall emotional risks; • Potential benefits in mood stabilization in women without a psychiatric history. | 12 |

*Source: Authors (2025).*

**Table 2: Type of OC**

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| --- | --- | --- |
| **Type of OC** | **Impacts** | **References** |
| Combined OCs (Estrogen + Progestin) | Associated with lower risk of emotional changes; variation depends on estrogen dose. | 11 |
| Progestin-Only OCs | • Higher prevalence of depressive and anxious symptoms; • Significant interaction with the stress system. | 13 |
| Monophasic vs. Multiphasic Formulations | Monophasic formulations associated with greater emotional stability than multiphasic ones. | 5 |

*Source: Authors (2025).*

**Table 3: Genetic Predisposition**

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| --- | --- | --- |
| **Genetic Aspect** | **Impacts** | **References** |
| Genetic Polymorphisms | Changes in the FKBP5 gene may intensify effects on the HPA axis, increasing stress vulnerability. | 6 |
| Family History of Mental Disorders | Family history is associated with higher risk of emotional changes due to genetic predisposition. | 15 |
| Gene-Hormone Interaction | Interaction with genes that modulate neurotransmitters such as serotonin and GABA may amplify psychological effects. | 15 |

*Source: Authors (2025).*

**Table 4: Interactions with Other Factors**

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| --- | --- | --- |
| **Contextual Factors** | **Description** | **References** |
| Sleep Disorders | Insomnia associated with OC use may exacerbate anxiety symptoms, creating a harmful cycle. | 7 |
| Lifestyle and Stress | Stress, workload, and social support can amplify or mitigate the effects of OCs. | 7 |

*Source: Authors (2025).*

1. **DISCUSSION**

**Impact on Different Age Groups**

Adolescents appear particularly vulnerable to the psychological effects of oral contraceptives (OCs). Studies suggest that OC use during adolescence may be linked to an increased risk of depression in adulthood. The developing brain is highly sensitive to hormonal fluctuations, and synthetic hormones may interfere with the regulation of neurotransmitters involved in emotional stability. Research has demonstrated that adolescent OC users report higher rates of mood swings, irritability, and depressive symptoms compared to non-users. Furthermore, prolonged OC use initiated during adolescence has been associated with long-term alterations in stress response, potentially predisposing individuals to mental health disorders later in life. In contrast, adult women, particularly those without a psychiatric history, tend to experience greater emotional stability with OC use. Some studies suggest that combined OCs (estrogen + progestin) may have a stabilizing effect on mood in this population. However, women with pre-existing anxiety or depressive disorders may still experience exacerbation of symptoms, indicating the need for individualized contraceptive counseling (2, 3, 15).

**Differences Between Combined and Progestin-Only Contraceptives**

The psychological impacts of OCs vary significantly based on their hormonal composition. Combined OCs, which contain both estrogen and progestin, are frequently associated with mood stabilization in some users, particularly those without a history of psychiatric disorders. Estrogen is known to have neuroprotective effects and has been linked to enhanced serotonergic activity, which can contribute to emotional well-being. In contrast, progestin-only contraceptives have been consistently linked to a higher prevalence of depressive and anxious symptoms. Progestins can have androgenic effects, which may counteract estrogen's mood-stabilizing properties and lead to an increased risk of mood disturbances. Some studies suggest that high-progestin formulations are more likely to induce negative emotional symptoms, whereas formulations with lower androgenic activity may be better tolerated. Additionally, monophasic formulations, which provide a consistent hormone dose throughout the cycle, appear to be associated with fewer mood fluctuations compared to multiphasic formulations that alter hormone levels at different phases of the cycle. These findings highlight the importance of selecting an appropriate OC formulation based on an individual’s psychological and hormonal profile to minimize adverse effects while preserving contraceptive efficacy (5, 12, 13).

**Genetic Interactions and Psychiatric Predisposition**

Genetic predispositions significantly influence the emotional impact of OCs. Women with a family history of mood disorders or specific genetic polymorphisms, such as variations in the FKBP5 gene, may have altered stress responses when using hormonal contraceptives. The FKBP5 gene plays a crucial role in regulating the HPA axis, which governs the body's response to stress. Women with certain FKBP5 variations may experience exaggerated cortisol responses, making them more vulnerable to anxiety and depression when exposed to synthetic hormones. Furthermore, the interaction between OCs and neurotransmitters such as serotonin and GABA may further contribute to psychiatric symptoms in genetically predisposed individuals. Research has indicated that OCs can alter serotonin receptor sensitivity, potentially exacerbating symptoms in women already predisposed to mood disorders. Genetic screening and psychiatric history assessments could help identify individuals at higher risk for OC-induced mood disturbances, enabling healthcare providers to recommend alternative contraceptive options or closer monitoring of psychological symptoms (6, 10, 13, 15).

**Clinical Recommendations**

Given the variability in psychological responses to OCs, individualized prescription strategies are necessary. Women with a personal or family history of depressive or anxious disorders should undergo thorough evaluations before initiating OC use. Healthcare providers should assess baseline mood symptoms, discuss potential side effects, and ensure that patients are aware of possible emotional changes associated with different contraceptive formulations. Regular monitoring of mood symptoms is crucial, particularly in the first few months of OC use, as some individuals may experience an adjustment period before symptoms stabilize. If significant adverse effects arise, alternative contraceptive options, such as non-hormonal methods or formulations with lower progestin activity, should be considered.

Adolescents, in particular, should receive counseling on potential mood-related side effects, and non-hormonal alternatives may be explored in high-risk cases. Given the heightened sensitivity of the developing brain to synthetic hormones, careful consideration should be given before prescribing OCs to adolescent users. In cases where hormonal contraception is necessary, healthcare providers may prioritize combined OCs with lower androgenic activity to minimize mood disturbances. Additionally, integrating genetic screening into contraceptive counseling could further refine personalized approaches to OC prescription, improving both mental health outcomes and patient satisfaction. Future research should focus on understanding the long-term impact of hormonal contraception on mental health and identifying strategies to optimize contraceptive choices for women with psychiatric vulnerabilities (6, 10, 13, 16).

1. **CONCLUSION**

The study identified that the effects of oral contraceptives (OCs) vary widely based on factors such as age, type of contraceptive, and mental health history. Adolescents were consistently highlighted as a vulnerable group, with evidence indicating an increased risk of depression in adulthood associated with OC use during this phase of life. In contrast, adult women, especially those without psychiatric histories, demonstrated greater emotional stability with the use of combined contraceptives. Combined OCs (estrogen + progestin) exhibited mood-stabilizing effects in some contexts, while progestin-only contraceptives were more strongly associated with adverse symptoms such as increased anxiety and depression. These effects can be explained by alterations in the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmission, affecting systems like serotonin and GABA.

Additionally, impact patterns related to hormonal stability were identified. Monophasic formulations, which provide consistent hormone doses, were associated with fewer emotional fluctuations than multiphasic formulations. Women with genetic predispositions or a family history of mental disorders showed greater vulnerability, reinforcing the need for clinical monitoring. On the other hand, potentially positive effects were observed in subgroups without psychiatric histories, where OCs helped reduce emotional variability and stabilize mood, particularly in contexts involving hormonal regulation.

These findings emphasize the importance of a personalized approach to prescribing OCs, considering individual characteristics and vulnerable subgroups. The review also highlighted significant gaps, such as the need for more longitudinal studies to assess long-term impacts and explore underlying biological mechanisms.]

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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