

Correspondence: mynair@ucsc.edu

Keywords:

oral contraceptives (OC) depression estrogen progesterone synaptic pruning prefrontal cortex hypothalamic-pituitary-adrenal (HPA) axis

Submitted December 11, 2023 Accepted July 14, 2024 Published December 27, 2024

Long-Term Effects of Hormonal Oral Contraceptives on Adolescents' Mental Health

By: Mythili Nair, Isabelle Pappas, and Sahithi Lingala



Abstract

Adolescence is a critical stage of development marked by profound physical, emotional, and psychological changes. During this period, many adolescents turn to contraceptives for various reasons, including birth control, menstrual regulation, and addressing medical conditions. However, the potential impact of contraceptives on the mental health of adolescents remains a topic of significant concern and debate. This paper serves as a review of current literature on oral contraceptives (OCs), which are the most commonly prescribed form to adolescents, and concentrates on research that correlates contraceptives with heightened depression symptoms. The synthesis of findings in this review aims to inform healthcare professionals and researchers about the importance of further research and to help young individuals acquire a deeper comprehension of the long-term mental health implications associated with OC use during adolescence.

1. Introduction

This paper aims to delve into the pharmacological and psychological mechanisms of oral contraceptives and their role in the onset or exacerbation of depression in adolescents. It will examine scientific reviews and primary articles to discuss how oral contraceptives work and alter adolescent physiology. Additionally, it will provide insights into what depression is and how SSRIs and oral contraceptives can interact. This paper serves as an information guide for adolescents, raising awareness about the effects of birth control and emphasizing their increased vulnerability to depressive symptoms. It also serves as a call to action, advocating for further research to create effective contraceptive methods with a reduced risk of mood disorders.

Contraceptives encompass a diverse range of devices and drugs designed to prevent pregnancy, and they also serve several purposes like menstrual regulation, pain management, and addressing medical concerns such as endometriosis. In today's market, contraceptives are broadly categorized into two main groups: hormonal and non-hormonal. Hormonal birth control includes emergency contraception (typically in pill form), oral contraceptives, implants, the vaginal ring, and estrogen/progestin patches. Hormonal contraceptives function by introducing synthetic hormones that mimic the body's naturally occurring sex hormones, estrogen, and progesterone. Oral contraceptives are taken daily by mouth, while implants, rings, and patches are placed inside the body and slowly release hormones into the bloodstream.¹

Non-hormonal birth control methods consist of condoms, spermicides, and natural family planning/fertility awareness. Condoms, which can be made of latex, polyurethane, or lambskin, act as a barrier to prevent sperm from entering the uterus. Spermicides are chemical agents that kill or immobilize sperm, often used in conjunction with other barrier methods. Family planning involves cycle tracking and avoiding intercourse during ovulation to prevent unwanted pregnancy. Additionally, intrauterine devices (IUDs) are a popular choice, available in both hormonal (progestin IUD) and non-hormonal (copper IUD) variations. The progestin IUD functions similarly to other hormonal contraceptives, while the copper IUD creates a toxic environment for sperm, effectively killing them before fertilization.¹

In 2018, a study unveiled that 38.7% of adolescents utilized contraception for medical purposes and to prevent unwanted pregnancies. Among the various options, oral contraceptives stood out as the most frequently prescribed for young women due to their effectiveness and user-friendly nature.² Typically, the combination pill, incorporating both estrogen and progesterone, constitutes the most prevalent type, administered over a 28-day cycle comprising 21 active pills followed by a week of placebos, inducing menstruation. Doses are personalized by physicians upon prescription. These pills work by mimicking a pregnancy-like state, fooling the pituitary gland into halting hormone release for ovulation, thus preventing pregnancy. Progesterone, meanwhile, thickens cervical mucus, hampering sperm access to the uterus, and alters the uterine lining, impeding egg attachment. While crucial for maintaining stable hormone levels and aiding in addressing medical conditions, the introduction of synthetic hormones can disrupt the body's natural equilibrium, leading to various side effects. It is especially vital to discuss these potential effects with adolescents, given their heightened susceptibility to hormonal and bodily changes.3

Among these side effects, the deterioration of mental health and worsening of mood disorders is one of the most studied. Over the years, multiple studies have explored the correlation between oral contraceptives and depression, particularly in adolescents.⁴ Depression has been linked to low serotonin, dopamine, and norepinephrine levels, influenced by genetic predisposition rather than solely inheritance. To address depression, selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed, enhancing serotonin transmission by blocking its reabsorption into neurons. It is worth noting that SSRIs can also impact estrogen and progesterone levels due to their interaction with the body's hormones, potentially affecting those using both antidepressants and birth control. In adolescents, the onset of depression is associated with increasing levels of gonadal hormones, including estrogen and progesterone. Contraceptive pills introduce synthetic sex hormones into the body, potentially elevating these hormone levels and worsening depression symptoms. The connection between depression and oral contraception remains a subject of ongoing research.⁵



Figure 1. A Visual Representation of the Different Types of Contraceptives. The figure highlights the distinctions between oral contraceptives, implants, IUDs, and barrier methods, emphasizing their mechanisms and clinical applications. This visualization underscores the diverse choices available for managing reproductive health.

2. Literature Review

2.1 Studies Show that the Link Between OC Use and Depression in Women is Not Entirely Straightforward

The link between oral contraceptive pill (OCP) use and depression is not entirely straightforward and has been a topic for debate for decades since the conception of the pill. More recent studies (from 2020 onward) tend to agree that oral contraceptive use can cause depressive symptoms in those with no history of psychiatric illness as well as exacerbate symptoms in those with a history of mental illness. According to a pilot study conducted by Jayashri Kulkarni, depressive symptoms that result from oral contraceptive use was the single most reason for discontinuation of the pill.⁶ However, there are several earlier studies that show no correlation between OCP use and depressive symptoms, suggesting that our knowledge about the link between the two is limited. B. Bottcher et al. analyze several studies from 1960-2005 that examine the effects of OCP use on mood. Bottcher et al. contribute the misattribution of OCP use to depression with "the inconsistent use of the term 'depression' and the large number of combined contraceptives which vary in their compositions."⁷ According to the DSM, "A major depression is not equivalent to negative mood changes, tension, irritability, anxiety, or sadness," and, as a result, the results of the studies analyzed in this article do not necessarily indicate OCP use as a cause of depression.⁸ Bottcher et al. also claim that depression is more common in women than it is in men, and the "median age for diagnosis was 31, which is within the reproductive age."9 Thus, it may not be entirely true that OCP use directly causes depression but rather that women are more likely than men to show signs of depressive symptoms. Additionally, the majority of women who use oral contraceptives are likely to be of reproductive age, which is the most common age at which depression is diagnosed in both women and men. Ultimately, B. Bottcher at al. concluded that there is no significant correlation between OCP use and depressive symptoms. That being said, Bottcher et al. also recognize the limitations of their analysis, as "the composition of hormonal contraceptives has also changed dramatically- the dose of ethinyl estradiol has been consistently reduced over the years and is less than half of that used in the early years of hormonal contraception."¹⁰ The researchers analyzed studies from around the late 20th century, and the compositions of present-day OCPs have changed significantly since then. This change may have something to do with the conflicting results in later studies that often find a correlation between OCP use and depression in women.

Another study conducted by T. Johannson et al. examined the long-term mental health effects of birth control on women and found that OCP use is "causally" related to risk of depression. The study utilized medical information from more than 250,000 women in the UK Biobank (UKB) and looked particularly at the risk of depression in adolescents and adults during and after OCP use. The study found that "the first 2 years of OC use were associated with a higher rate of depression compared to never users."¹¹ Even more, their findings "showed that women who used OCs during adolescence remained at a heightened risk even after they discontinued, whereas such a risk was not apparent among adult OC users.^{*12} Johannes et al. explain the results of their findings by suggesting that adolescents are more sensitive to hormonal changes, putting them at an increased risk for depression with OCP use. According to Johannson, sensitivity to hormonal changes is greatest "during crucial developmental periods that affect the organization of the brain structures and may lead to long-lasting changes.^{*13} This article confirms the causal relationship between OCP use and an increased risk of depression in adolescents. However, the researchers' discussion of their results suggests that adolescents are inherently vulnerable to depressive symptoms due to puberty and environmental changes and that OCP use may only exacerbate these symptoms.

While T. Johannson et al. discovered a causal relationship between an increased risk of depression and OCP use, a study conducted by Anouk E. de Wit et al. (2021) suggests that it is not clear whether the relationship is causal or not. The researchers conducted a meta-analysis of clinical trials consisting of over 5000 women who were given either a hormonal contraceptive pill or a placebo pill. Only one trial consisted of adolescent women; thus, the researchers concluded that they "cannot rule out that first-time use is a risk factor for experiencing depressive symptoms with hormonal contraceptive use."14 The hormonal contraceptives that were given to the women included combined oral contraceptive pills, pills, contraceptive patches, combined injectable progestin-only contraceptives, progestin-only injectable contraceptives, intrauterine devices, and more. Thus, the pill was not the only hormonal contraceptive method that was studied here but also other forms of hormonal contraception, like the patch and injectables. The results of the study suggest that not a single form of hormonal contraception showed a greater risk of depression over another or the placebo. This conclusion is in direct opposition to that of several observational studies, which have found a significant increase in incidence of depression in OCP users and particularly in adolescent OCP users.¹⁵

A year earlier, the same researcher Anouk E. de Wit co-authored a different article that looked at the association of oral contraceptive use with depressive symptoms among young women and adolescents. The researchers "did not find support for an overall association between OCP use and depressive symptoms among young women. However, 16 year old girls using OCPs did report higher concurrent depressive symptom scores compared with their nonusing counterparts."16 16-year-old users of OCPs reported a greater incidence of crying, hypersomnia, and eating problems, which symptoms are more associated with adolescent depression as opposed to adult depression. The researchers also discuss several confounding variables that may explain this trend. Anouk de Wit et al. suggest that there may be a higher prevalence of depression in 16-year-old OCP users not only due to the hormonal changes that the drug itself induces but also because "treatment with OCPs is standard care for cycle-related mood problems and for polycystic ovarian syndrome, which is associated with depressive symptoms."¹⁷ Thus, the increased prevalence of depression in 16 year-old OCP users as compared to nonusers of that same age group might be related to the fact that those 16 year-olds who use OCPs are more likely to have suffered from depression and other mood disorders even before they started the pill.

In an article published in 2004, Stephen A. Robinson et al. set out to determine whether psychological or pharmacologic mechanisms were responsible for the adverse emotional side effects of the pill in OC users. The researchers conducted a study in which half of the women were given OC pills and the other half placebo pills. The results of study show that women on the placebo pill "experienced a similar side effect profile of OCP users."¹⁸ Psychiatrist Johan Culberg proposed that the psychological side effects of OC use were due to the "symbolic property of contraception:" "it is something that prevents sexual intercourse from being followed by pregnancy and an unwanted child."19 Additionally, the blood levels of estrogen and progesterone in the OCP users were measured, and researchers found no significant correlation between hormone blood levels and depressive symptoms in these women. This is to suggest that the adverse mental and emotional side effects from OC use are largely due to psychological, not pharmacologic, mechanisms. Robinson et al. conclude, "it is not the pharmacodynamics that primarily impact the individual's psyche and subsequent emotions and behavior, but rather the belief that one is contracepting is causing such a phenomenon."²⁰ Additionally, the

authors introduce the idea that "contraception leads to a complete dissociation from the pleasurable/ relational and procreational components which, in turn, places a different value on sexuality itself."²¹

It turns out that the use of oral contraceptives is not the only factor that changes the "value of sexuality." In fact, the "value of sexuality" has been changing since the sexual revolution of the 60s and, even more so, with the advent of the modern hook-up culture. According to an article published by Justin R. Garcia et al. in the National Library of Medicine, "hook-ups" are defined as "uncommitted sexual encounters [which] are becoming progressively more ingrained in popular culture, reflecting both evolved sexual predilections and changing social and sexual scripts."22 Since sexual encounters are becoming more non-committal, and, thus, more frequent, the use of products such as oral contraceptives to prevent lifelong consequences is much more prevalent today than it was even only a decade ago. As such, there have been several articles published within the last four years that aim to discuss both the physical and mental-emotional side effects of oral contraceptives in women, particularly adolescents. Perhaps this is why more recent studies, by de Wit et al. in 2020-21 and by Johannson et al. in 2023, are largely focused on the effects of OC use in adolescent women or first time users as compared to older women or women who have been using OCs for more than two years. As it turns out, all scientific inquiries are influenced by the social phenomena that plague the particular period of time in which they are made.

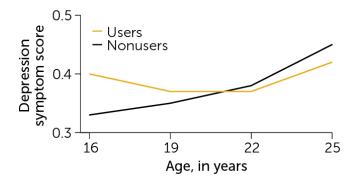


Figure 2. A Graphical Representation of the Correlation Between Oral Contraceptive Use and the Prevalence of Depression in Adolescent Users. OC users have a higher depression symptom score from approximately ages 16 to 21 than do non-users. A higher depression symptom score indicates more depression symptoms

overall. The graph highlights the higher risk during the first two years of use, providing evidence of increased vulnerability in younger populations.

2.2 Chemistry/ Pharmacology of Oral Contraceptives Associated with Depressive Symptoms in Adolescent Users

Oral contraceptive pills (OCPs) are a commonly used form of birth control, and while they are generally considered safe and effective, there is growing concern regarding their potential link to mood disorders, particularly in adolescent users. To understand the plausible chemical and pharmacologic explanations for depression in adolescent OCP users, it is essential to examine the intricate relationship between the hormones present in these pills, namely estrogen and progesterone, and their impact on neurochemistry and brain function.

These hormones exert their effects through specific receptors, with estrogen acting primarily through estrogen receptors (ER)-alpha and ER-beta, and progesterone through progesterone receptors alpha and beta, distributed throughout the brain. ER-alpha is prominently found in the hypothalamus, hippocampus, amygdala, and brainstem,34 while progesterone receptors alpha and beta are most abundant in the amygdala, cerebellum, cortex, hippocampus, and hypothalamus.³⁵ Estrogen, in particular, has been associated with neuroprotection in various regions of the brain, such as the hypothalamus, hippocampus, amygdala, and brainstem. Several studies have suggested that estrogen can safeguard the brain against neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, cognitive decline, and affective disorders.³⁶ Functional brain imaging studies have revealed that estrogen plays a role in regulating the activation of brain regions involved in emotional and cognitive processing, such as the amygdala and dorsolateral prefrontal cortex.³⁷ Additionally, in animal studies, estrogen has been shown to modulate several neurotransmitters, including serotonin, dopamine, and noradrenaline, all of which have significant implications for mood regulation and depression. Estrogen can also influence the release of adrenocorticotropic hormone, further impacting stress responses and mood.³⁸

In contrast to estrogen, progesterone does not exhibit the same neuroprotective properties. In fact, evidence suggests that progesterone can exacerbate mood symptoms and potentially contribute to the development of mood disorders. Plausible mechanisms for this include progesterone's augmentation of GABA-induced inhibition of glutamate transmission and its ability to increase the concentrations of monoamine oxidase. These actions can lead to decreased serotonin levels, which are often associated with depressive symptoms.³⁹ Moreover, a study has shown a positive association between the use of levonorgestrel-containing intrauterine devices (IUDs) and the development of depression, anxiety, and sleep problems in women who did not have these conditions before using the IUD.⁴⁰ Levonorgestrel is a synthetic progestogen, and the two formulations of progestogen-releasing IUDs, containing 19.5 mg and 52 mg of levonorgestrel, may have varying effects on mood.⁴¹ The former, which releases smaller amounts of levonorgestrel, may be more tolerable in terms of mood disturbances. However, it is crucial to note that there is a lack of comprehensive data regarding the relationship between this specific IUD and the development or exacerbation of depression.

Selective Serotonin Reuptake Inhibitors (SSRIs) and oral contraceptives can have notable interactions when used concurrently, which is essential to consider for individuals who are prescribed both medications. SSRIs, commonly used to treat depression and anxiety disorders, work by increasing the levels of serotonin in the brain, a neurotransmitter that affects mood and emotional state.⁴² On the other hand, oral contraceptives contain synthetic hormones, typically a combination of estrogen and progestin, which are used for birth control and to regulate menstrual cycles.⁴³ When taken together, these medications can influence each other's metabolism and effectiveness. For instance, some SSRIs can increase the levels of estrogen in the body by inhibiting enzymes responsible for estrogen metabolism. This elevation could potentially increase the risk of side effects associated with oral contraceptives, such as blood clots, especially in individuals with other risk factors. Conversely, certain oral contraceptives can affect the metabolism of SSRIs, potentially altering their efficacy and leading to either increased or decreased levels of the antidepressant in the bloodstream. This interaction might necessitate adjustments in SSRI dosages to maintain therapeutic effectiveness and minimize side effects.44 It's crucial for individuals taking both SSRIs and oral contraceptives to have close

monitoring by healthcare professionals to manage these potential interactions effectively.

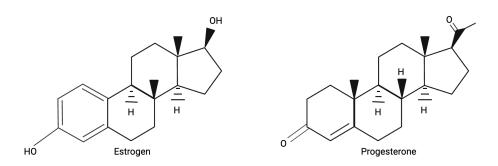


Figure 3. Molecular Structures of Estrogen and Progesterone, the Primary Hormones in Oral Contraceptives. The figure demonstrates their chemical composition and structural differences, helping to explain their unique roles in contraceptive efficacy and potential effects on mood regulation.

3. Discussion

3.1 Higher Risk of Depression in Adolescents

Adolescence is a period marked by a higher risk of depression, a risk deeply rooted in biological factors. Firstly, the ongoing development of the adolescent brain plays a crucial role. During this stage, the brain undergoes synaptic pruning, a process that eliminates unnecessary connections to increase efficiency. This phase involves the removal of neural connections that are less frequently used, while strengthening those that are more active. This selective pruning helps in optimizing brain efficiency and functionality. However, it is important to note that this process is not uniform across the brain. Different areas of the brain undergo this pruning at different times, which can lead to imbalances in cognitive and emotional processing during adolescence.²³ Additionally, the prefrontal cortex, a part of the brain responsible for higher-order functions like decision-making, impulse control, and emotional regulation, is one of the last areas to mature. This delayed development can contribute to characteristic adolescent behaviors. Adolescents might struggle with impulse control, making them more prone to risk-taking behaviors. They might also experience challenges in decision-making, leading to choices that seem irrational or poorly

thought out from an adult perspective.²⁴ The combination of an underdeveloped prefrontal cortex and ongoing synaptic pruning can lead to heightened emotional experiences in adolescents. They might face difficulties in managing their emotions, leading to mood swings or intense emotional reactions to situations that adults might find more manageable. This heightened emotional sensitivity is often compounded by hormonal changes that occur during puberty, further complicating the emotional landscape of adolescence.

The adolescent phase marks a significant surge in sex hormones, primarily estrogen in females and testosterone in males. These hormones do more than just drive physical development; they profoundly influence the brain's chemistry, particularly the neurotransmitter systems.²⁵ A key player in this scenario is serotonin, a neurotransmitter that plays a critical role in regulating mood and emotional well-being. The surge in sex hormones during adolescence directly impacts serotonin levels in the brain. Serotonin is known for its role in feelings of happiness and emotional stability, and its fluctuating levels can significantly affect an adolescent's mood. These hormonal changes can make adolescents more vulnerable to mood disturbances. For instance, a dip in serotonin levels can lead to feelings of sadness or a depressed mood, contributing to the increased incidence of depressive symptoms observed in this age group.²⁶ Notably, these hormonal fluctuations also interact with the adolescent's stress response system.

The which includes stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, becomes more reactive during adolescence. This heightened reactivity, combined with fluctuating serotonin levels, can make adolescents particularly sensitive to stress. They may experience more intense reactions to stressful situations, and their ability to cope with these stressors may be compromised due to the ongoing developmental changes in their brains. Moreover, these biological factors do not function independently. They are intricately connected to and influenced by the adolescent's environment, including their social interactions, family dynamics, and life experiences. Stressful or negative environments can exacerbate the impact of hormonal changes on mood and stress response, leading to a higher risk of developing mental health issues

such as anxiety or depression.²⁷ The intricate relationship between the hypothalamic-pituitary-adrenal (HPA) axis and adolescent development plays a pivotal role in understanding the increased vulnerability to stress and depression during this critical life stage. The HPA axis, a central part of the body's stress response system, becomes highly sensitive during adolescence. This sensitivity is largely due to the significant hormonal changes occurring during this period, which interact with and can potentially dysregulate the HPA axis. Typically, the HPA axis helps the body manage stress by releasing cortisol, a hormone that prepares the body to handle stressful situations. However, during adolescence, this system can become overactive or remain active for longer periods due to the heightened hormonal fluctuations. This dysregulation of the HPA axis in adolescents leads to an enhanced stress response, making them more reactive to stressors that might seem manageable to adults.

This heightened stress reactivity is not just a momentary experience; it can have prolonged effects on the adolescent's emotional and psychological well-being. The continual overexposure to cortisol and other stress hormones can lead to various adverse outcomes, one of the most concerning being an increased susceptibility to depression.²⁸ Adolescents, already dealing with various physical, social, and emotional changes, may find this added stress reactivity overwhelming, pushing them towards depressive states. Moreover, this heightened vulnerability is not just a matter of increased emotional sensitivity; it has biological underpinnings that can lead to long-term patterns of stress response and emotional regulation. The ongoing stress and potential for depression during adolescence can, in turn, affect the brain's development and functioning, particularly in areas responsible for mood regulation and stress management. This creates a feedback loop where dysregulation of the HPA axis exacerbates stress and depression, which further affects the HPA axis's functioning.²⁹

Importantly, these biological processes do not exist in isolation; they are closely intertwined with the social and environmental factors that adolescents face. Peer relationships, academic pressures, family dynamics, and the quest for self-identity all influence an adolescent's emotional well-being.³⁰ A biological predisposition to depression refers to the inherent

tendency, often influenced by genetic and physiological factors, that makes certain individuals more susceptible to developing depression compared to others. Genetics indeed play a significant role in this predisposition.³¹ Research has identified several genes associated with an increased risk of depression, although it is important to note that no single gene causes the disorder. Instead, depression is a complex trait influenced by multiple genes, each contributing a small effect. These genes often affect neurotransmitter systems in the brain, such as serotonin, dopamine, and norepinephrine pathways, which are crucial for mood regulation.³² In adolescents, the interplay between these genetic predispositions and the rapid physiological changes they undergo becomes particularly impactful. The brain is still developing during adolescence, and hormonal fluctuations are significant. These hormonal changes can influence the expression of genes related to mood regulation and stress response, potentially triggering or exacerbating depressive symptoms in those with a genetic predisposition.³³ Understanding these intricate biological underpinnings is essential in developing effective interventions and support systems to help adolescents navigate this challenging period and reduce the risk of depression.

3.2 Practical Applications

The following section discusses the practical applications of the research that attempts to demystify the mental health effects of oral contraceptives on adolescents. Since the sexual revolution in the 60s, the stigma surrounding sexual health and pleasure has declined significantly. The advent of a hook-up culture in more recent years means that women are having sexual experiences at a younger age today than ever before. Of course, the value of sex has changed over time as well, as more women choose to engage in sex acts not only for procreative purposes but also for pleasure. Patentors of birth control packaging should make a clear list of not only the physical but also the mental-emotional side effects of the pill on its packaging. With the recent rise in abortion bans across the US, administering safe and effective forms of birth control to adolescent women is more important now than ever before.¹ More recently, the FDA approved a non-prescription, over-the-counter birth control pill The Opill, to be released in early 2024.² This means that birth control will be much more

accessible to women of all age groups. Adolescents may benefit most from The Opill as neither a prescription nor parental consent will be required to obtain birth control. Since adolescents will soon have easier access to hormonal contraception, it is particularly important to educate adolescents on the mental and emotional side effects of the pill. Additionally, before prescribing birth control pills to their patients, healthcare providers should take into account the psychiatric history and age of their OC candidates. Both parties, the prescriber and the patient, need to be informed of the physical and mental side effects of the oral contraceptive they choose to administer and take, respectively, as if it were any other drug. Knowledge about the ways in which both prescription and non-prescription medication can affect our emotional-well-being is paramount to using hormonal contraceptive safely and effectively.



Figure 4. The Opill, a Progestin-Only Birth Control Pill Now Available Over the Counter. This marks a major step forward in making contraception more accessible and empowering individuals to take charge of their reproductive health.

4. Future Directions

Scientists are engaged in extensive research and development efforts to address the risk of depression and mood disorders associated with oral contraceptive pills. One promising avenue involves fine-tuning the hormone formulations in these contraceptives. By modifying the types and quantities of hormones, researchers aim to create pills with reduced mood-altering effects while maintaining their effectiveness in preventing pregnancy. For instance, scientists are working on progestins with a lower propensity to affect mood.⁴⁷ Additionally, the use of transdermal patches or hormonal intrauterine devices (IUDs) is being explored as alternative delivery methods that might limit systemic hormone exposure and, consequently, mood-related side effects. Personalized medicine is emerging as a key strategy. Researchers are investigating ways to identify genetic, hormonal, and psychological factors that make certain individuals more susceptible to mood disturbances when using oral contraceptives.⁴⁸ This approach allows healthcare providers to match women with contraceptives that are less likely to negatively impact their mood based on their unique profiles.

To delve deeper into this issue, scientists are conducting extensive research into the mechanisms underlying the connection between hormonal contraceptives and mood disorders. This includes studying how these medications affect the brain, neurotransmitter systems, and the endocrine system. By understanding the exact mechanisms at play, researchers can develop more targeted interventions and, ideally, identify biomarkers that can predict which individuals are at a higher risk of experiencing mood-related side effects. Furthermore, the future of contraceptive care is set to encompass behavioral and psychological support. Integrated counseling, resources, and strategies will be provided to women both before and during contraceptive use, empowering them to manage mood changes and mental health concerns more effectively. This support can include coping strategies, stress management techniques, and interventions to address any mood disturbances that may arise.⁴⁹ Long-acting contraceptives are gaining attention as alternatives for some women. Hormonal IUDs and implants release hormones in a more controlled and localized manner, potentially reducing the systemic impact on mood. Researchers are working on expanding the availability and improving the safety of these long-acting options.⁵⁰ In this digital age, telemedicine and digital health tools are becoming invaluable. They enhance access to healthcare providers and mental health resources for women using oral contraceptives. Real-time monitoring and digital platforms can facilitate early identification of mood changes and enable timely interventions, contributing to improved mental well-being during contraceptive use.

4. Conclusion

In conclusion, this review paper has addressed the critical issue of the long-term effects of hormonal oral contraceptives on adolescents' mental health. The research highlights the complex and multifaceted relationship between oral contraceptives and mood disorders, particularly in adolescent users. While the topic remains a subject of debate, it is clear that various factors, both biological and psychological, can contribute to the development or exacerbation of depressive symptoms. This paper has shed light on the biochemical processes at play, elucidating how hormones like estrogen and progesterone interact with the brain, potentially impacting mood regulation. It has also explored the role of psychological mechanisms, demonstrating that beliefs and societal attitudes about contraception can influence emotional well-being. Furthermore, the increased vulnerability of adolescents to mood disorders, owing to ongoing brain development, hormonal fluctuations, and heightened stress reactivity, has been discussed. The interplay between biological factors and the social and environmental challenges that adolescents face underscores the need for comprehensive support and interventions to mitigate the risk of depression during this crucial stage of development.

Looking ahead, scientists and healthcare providers are actively pursuing strategies to minimize the potential risks of hormonal contraceptives, emphasizing personalized medicine, alternative delivery methods, and the integration of behavioral and psychological support. Long-acting contraceptives and digital health tools are emerging as promising options to enhance mental well-being for contraceptive users. As we move into the future, it is imperative to continue research in this field to gain a more comprehensive understanding of the implications of oral contraceptive use on adolescents' mental health. The goal is to provide young individuals with safer and more effective contraceptive choices while prioritizing their emotional and psychological well-being. With an informed approach and tailored interventions, we can empower adolescents to make educated decisions about their reproductive health, ultimately leading to improved mental health outcomes.

References

1. Mayo Clinic. Birth control options: Things to consider. *Mayo Clinic*. 2022 Feb 16. https://www.mayoclinic.org/healthy-lifestyle/b irth-control/in-depth/birth-control-options/ar t-20045571. Accessed 2024 Dec 5.

2. Centers for Disease Control and Prevention (CDC). Products - Data Briefs - Number 388. 2020 Dec 8. Accessed 2023 Dec 10. https://www.cdc.gov/nchs/products/databriefs /db388.htm.

3. NHS. Combined pill. *NHS.uk.* 2017 Dec 21. https://www.nhs.uk/conditions/contraception/c ombined-contraceptive-pill.

4. Mu E, Kulkarni J. Hormonal contraception and mood disorders. *Aust Prescr.*2022;45(3):75-79. doi:10.18773/austprescr.2022.025.

5. Derntl B. The impact of hormonal contraceptive use on serotonergic neurotransmission and antidepressant treatment response: Results from the NeuroPharm 1 study. *Front Psychol.* Published online. Accessed 2024 Dec 5.

6.Kulkarni J. Depression as a side effect of the contraceptive pill. *Expert Opin Drug Saf.* 2007;6(4):371. doi:10.1517/14740338.6.4.371.

7. Böttcher B, Radenbach K, Wildt L, Hinney B. Hormonal contraception and depression: A survey of the present state of knowledge. *Arch Gynecol Obstet.* 2012;286(1):231. doi:10.1007/s00404-012-2298-2.

8. Böttcher B, et al. Depression as a side effect of the contraceptive pill. *Arch Gynecol Obstet.*

2012;286(1):235.

9. Böttcher B, et al. Depression as a side effect of the contraceptive pill. *Arch Gynecol Obstet.* 2012;286(1):232.

 Böttcher B, et al. Depression as a side effect of the contraceptive pill. *Arch Gynecol Obstet*.
 2012;286(1):232–235.

11. Johansson T, Vinther Larsen S, Bui M, Ek
WE, Karlsson T, Johansson Å.
Population-based cohort study of oral contraceptive use and risk of depression. *Epidemiol Psychiatr Sci.* 2023:1.
doi:10.1017/s2045796023000525.

12. Johansson T, et al. Population-based cohort study of oral contraceptive use and risk of depression. *Epidemiol Psychiatr Sci.* 2023:7.

13. Johansson T, et al. Population-based cohort study of oral contraceptive use and risk of depression. *Epidemiol Psychiatr Sci.* 2023:6.

14. de Wit AE, de Vries YA, de Boer MK, et al. Hormonal contraceptive use and depressive symptoms: Systematic review and network meta-analysis of randomized trials. *BJPsych Open.* 2021;7(4):8. doi:10.1192/bjo.2021.64.

15. de Wit AE, et al. Hormonal contraceptive use and depressive symptoms. *BJPsych Open*. 2021;7(4):1-11.

16. de Wit AE, Booij SH, Giltay EJ, et al. Association of use of oral contraceptives with depressive symptoms among adolescents and young women. *JAMA Psychiatry*. 2019;77(1):52-58. doi:10.1001/jamapsychiatry.2019.2838. 17. de Wit AE, et al. Association of use of oral contraceptives with depressive symptoms among adolescents and young women. *JAMA Psychiatry.* 2019;77(1):58.

 Robinson SA, Dowell M, Pedulla D, McCauley L. Do the emotional side-effects of hormonal contraceptives come from pharmacologic or psychological mechanisms? *Med Hypotheses.* 2004;63(2):268.

 Robinson SA, Dowell M, Pedulla D, McCauley L. Do the emotional side-effects of hormonal contraceptives come from pharmacologic or psychological mechanisms? *Med Hypotheses.* 2004;63(2):271.

20. Robinson SA, Dowell M, Pedulla D, McCauley L. Do the emotional side-effects of hormonal contraceptives come from pharmacologic or psychological mechanisms? *Med Hypotheses.* 2004;63(2):271.

21. Robinson SA, Dowell M, Pedulla D, McCauley L. Do the emotional side-effects of hormonal contraceptives come from pharmacologic or psychological mechanisms? *Med Hypotheses.* 2004;63(2):272.

22. Garcia JR, Reiber C, Massey SG, Merriwether AM. Sexual hookup culture: A review. *Rev Gen Psychol.* 2012;16(2):161. doi:10.1037/a0027911.

23. Spear LP. Adolescent neurodevelopment. *J Adolesc Health.* 2013;52(2):S7–S13. doi:10.1016/j.jadohealth.2012.05.006.

24. Arain M, Mathur P, Rais A, et al. Maturation of the adolescent brain. *Neuropsychiatr Dis Treat.* 2013;9(9):449–461. doi:10.2147/ndt.s39776.

25. Peper JS, Dahl RE. The teenage brain. *Curr Dir Psychol Sci.* 2013;22(2):134–139. doi:10.1177/0963721412473755.

26. Montoya ER, Terburg D, Bos PA, van Honk J. Testosterone, cortisol, and serotonin as key regulators of social aggression: A review and theoretical perspective. *Motiv Emot.*2011;36(1):65-73. doi:10.1007/s11031-011-9264-3.

27. Spear LP. Heightened stress responsivity and emotional reactivity during pubertal maturation: Implications for psychopathology. *Dev Psychopathol.* 2009;21(1):87-97. doi:10.1017/s0954579409000066.

28. Romeo RD. The teenage brain: The stress response and the adolescent brain. *Curr Dir Psychol Sci.* 2013;22(2):140-145. doi:10.1177/0963721413475445.

29. Karin O, Raz M, Tendler A, et al. A new model for the HPA axis explains dysregulation of stress hormones on the timescale of weeks. *Mol Syst Biol.* 2020;16(7). doi:10.15252/msb.20209510.

30.Twenge JM. Why increases in adolescent depression may be linked to the technological environment. *Curr Opin Psychol.* 2019;32:89-94. doi:10.1016/j.copsyc.2019.06.036.

31. Shadrina M, Bondarenko EA, Slominsky PA. Genetic factors in major depression disease. *Front Psychiatry.* 2018;9(334). doi:10.3389/fpsyt.2018.00334.

32. Lohoff FW. Overview of the genetics of major depressive disorder. *Curr Psychiatry Rep.* 2010;12(6):539-546.
doi:10.1007/s11920-010-0150-6.

33. Jiang S, Postovit L, Cattaneo A, Binder EB, Aitchison KJ. Epigenetic modifications in stress response genes associated with childhood trauma. *Front Psychiatry*. 2019;10(808). doi:10.3389/fpsyt.2019.00808.

34. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ER α) and beta (ER β): Subtype-selective ligands and clinical potential. *Steroids*. 2014;90:13-29. doi:10.1016/j.steroids.2014.06.012.

35. Brinton RD, Thompson RF, Foy MR, et al. Progesterone receptors: Form and function in brain. *Front Neuroendocrinol.*2008;29(2):313-339. doi:10.1016/j.yfrne.2008.02.001.

36. Koszegi Z, Cheong RY. Targeting the non-classical estrogen pathway in neurodegenerative diseases and brain injury disorders. *Front Endocrinol.* 2022;13. doi:10.3389/fendo.2022.999236.

37. Hara Y, Waters EM, McEwen BS, Morrison JH.
Estrogen effects on cognitive and synaptic health
over the life course. *Physiol Rev.*2015;95(3):785-807.
doi:10.1152/physrev.00036.2014.

38. Mu E, Kulkarni J. Hormonal contraception and mood disorders. *Aust Prescr.*2022;45(3):75-79.
doi:10.18773/austprescr.2022.025.

39. Standeven LR, McEvoy KO, Osborne LM.
Progesterone, reproduction, and psychiatric illness. *Best Pract Res Clin Obstet Gynaecol.*2020;69:108-126.
doi:10.1016/j.bpobgyn.2020.06.001. 40. Slattery J, Morales D, Pinheiro L, Kurz X. Cohort study of psychiatric adverse events following exposure to levonorgestrel-containing intrauterine devices in UK general practice. *Drug Saf.* 2018;41(10):951-958. doi:10.1007/s40264-018-0683-x.

41. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. *Contraception.* 2002;65(2):129-132. doi:10.1016/s0010-7824(01)00302-x.

42. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. *J Affect Disord.* 1998;51(3):215-235. doi:10.1016/s0165-0327(98)00221-3.

43. Cooper DB, Mahdy H, Patel P. Oral contraceptive pills. *PubMed*. Published November 24, 2022. <u>https://www.ncbi.nlm.nih.gov/books/NBK43</u> 0882/.

44. Berry-Bibee EN, Kim MJ, Simmons KB, et al. Drug interactions between hormonal contraceptives and psychotropic drugs: A systematic review. *Contraception.*2016;94(6):650-667. doi:10.1016/j.contraception.2016.07.011.

45. Foster DG. New abortion bans will increase existing health and economic disparities. *Am J Public Health*. 2022;112(9):1276-1277. doi:10.2105/ajph.2022.306993.

46. FDA. FDA approves first nonprescription daily oral contraceptive. *FDA*. Published July 13, 2023.

https://www.fda.gov/news-events/press-annou ncements/fda-approves-first-nonprescription-d aily-oral-contraceptive.

47. Sivasankaran S, Jonnalagadda S. Advances in controlled release hormonal technologies for contraception: A review of existing devices, underlying mechanisms, and future directions. *J Control Release*. 2021;330:797-811. doi:10.1016/j.jconrel.2020.12.044.

48. Personalised and precision medicine for contraception. *Dama Health.* Published August 17, 2022. <u>https://damahealth.com/the-science/</u>.

49. Dehlendorf C, Krajewski C, Borrero S. Contraceptive counseling. *Clin Obstet Gynecol.* 2014;57(4):659-673. doi:10.1097/grf.00000000000005

50. Bahamondes L, Fernandes A, Monteiro I, Bahamondes MV. Long-acting reversible contraceptive (LARCs) methods. *Best Pract Res Clin Obstet Gynaecol.* 2020;66:28-40. doi:10.1016/j.bpobgyn.2019.12.002.