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HORMONAL CONTRACEPTION AND THE RISK OF DEPRESSIVE SYMPTOMS: A LITERATURE REVIEW

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ABSTRACT

Introduction: Hormonal contraception (HC) is a method widely used for pregnancy prevention among adolescents and adult women. It is also prescribed to manage menstrual and dermatological symptoms. Despite its popularity, concerns have been raised regarding potential mental health side effects, particularly the risk of developing or worsening depressive symptoms. Existing research has produced mixed results—some studies suggest a possible association between HC use and an increased risk of depression, especially among younger users, while others report no significant link or even indicate a protective effect.

Aim of the Study: This literature review aims to evaluate current evidence regarding the relationship between HC use and the occurrence of depressive symptoms, with particular emphasis on adolescent girls and young women. By examining available research, the review seeks to clarify the potential psychological risks associated with different forms of hormonal contraception.

Conclusions: The findings of the cited studies suggest that the use of HC, especially during adolescence, may be associated with an increased risk of developing depressive symptoms. However, the evidence is not uniform—some studies do not confirm this negative effect, while others highlight the role of individual vulnerability. Further research is necessary to better understand the mechanisms underlying these associations and to support a more personalized approach to contraceptive counseling, particularly for young women at increased risk of mood disorders.

KEYWORDS

Hormonal Contraception, Oral Contraceptives, Combined Oral Contraceptives, Depression, Depressive Symptoms, Mental Disorders, Mood Disorders

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Introduction

Over the past few decades, hormonal contraception has become one of the most commonly used methods of pregnancy prevention in Poland, second only to male condoms. Globally, an estimated 150 million women use hormonal contraceptives (Kraft, M. Z. et al., 2024). However, this method is not without drawbacks, as it may cause various side effects. The most frequently reported include headaches, nausea and vomiting, breakthrough bleeding, and weight gain. Moreover, mood-related side effects constitute one of the main reasons for reluctance to start or continue oral hormonal contraception (OC). It is noteworthy that the lifetime prevalence of depression, including major depressive disorder (MDD), is approximately twice as high in women as in men (Albert, K. et al., 2021). This disparity is believed to be linked to the effects of key female sex hormones—estrogens and progestogens—on the central nervous system.

Clinical studies indicate that fluctuations in estrogen levels may contribute to the onset of depressive episodes, particularly in women predisposed to mood disorders. Lower estradiol levels have been observed in women diagnosed with major depression compared with healthy controls. Additionally, women who experience earlier menopause and whose hormone levels stabilize more quickly thereafter report fewer depressive symptoms. Possible mechanisms underlying these observations include the influence of progesterone metabolites that interact with GABA-A receptors, a major inhibitory pathway in the central nervous system. During the luteal phase of the menstrual cycle, levels of these neuroactive metabolites rise, which may lead to mood deterioration in some women (Mu, E., & Kulkarni, J., 2022). Furthermore, progestogens increase the activity of monoamine oxidase (MAO), an enzyme responsible for serotonin degradation, potentially contributing to depressive symptoms and irritability.

Oral contraceptives contain synthetic derivatives of these hormones. Synthetic ethinylestradiol, an analogue of natural estradiol, competes with endogenous estrogen receptors, while synthetic progestogens similarly mimic and compete with natural progesterone (Sondheimer, S. J., 2008). These progestogens are

categorized into generations based on chemical structure and pharmacological properties: first-generation (e.g., lynestrenol, norethisterone), second-generation (e.g., levonorgestrel, norgestrel), third-generation (e.g., desogestrel), and fourth-generation (e.g., dienogest). Each compound exhibits specific androgenic, estrogenic, or antiandrogenic activity, which is relevant when selecting an appropriate preparation according to a woman's age, lifestyle, personal preferences, and comorbidities (De Leo V. et al., 2016). Studies assessing the tolerability of combined oral contraceptives (COCs) with different progestogen generations have shown that formulations containing second-generation progestogens have lower discontinuation rates compared with first-generation agents (RR = 0.76; 95% CI: 0.67–0.86). Meanwhile, COCs containing third-generation progestogens may offer advantages in menstrual cycle regulation, such as a reduced risk of intermenstrual bleeding compared with levonorgestrel (RR = 0.71; 95% CI: 0.55–0.91) (Lawrie T. A. et al., 2011).

The mechanism of action of OCs involves inhibition of gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus and suppression of the anterior pituitary hormones FSH and LH through negative feedback. The consequences of this mechanism are associated with both reduced FSH and decreased LH levels. Suppression of FSH inhibits follicular growth and prevents the selection of a dominant follicle. Estrogen also affects procoagulant factor profiles by decreasing antithrombin III, increasing fibrinogen levels, and enhancing platelet aggregation. Lower LH levels prevent ovulation, while the progestogenic component thickens cervical mucus and decreases fallopian tube motility, hindering sperm transport to the ampulla of the fallopian tube, where fertilization typically occurs.

Two main types of oral hormonal contraceptives are distinguished: progestogen-only pills (POCs) and combined oral contraceptives (COCs), which contain both ethinylestradiol and a progestogen (De Leo V. et al., 2016). COCs—often referred to as the “micropill”—are usually taken in 21-day cycles with a 7-day break, mimicking natural menstrual patterns. They differ primarily in the type of progestogen used, with norethisterone, levonorgestrel, and dienogest being among the most common, each with distinct androgenic, estrogenic, or antiandrogenic profiles.

POCs—commonly known as the “minipill”—contain only a progestogen and are taken continuously without breaks. They are particularly recommended for breastfeeding women and for individuals in whom estrogen use is contraindicated or may cause adverse effects. Importantly, COCs are not recommended for women who smoke, due to increased cardiovascular risk (World Health Organization, 2015). Current formulations of POCs contain a variety of progestogens, including norethisterone and levonorgestrel—agents with moderate androgenic activity (Shoupe D., 2021).

Given the widespread use of hormonal contraception, its increasing popularity among adolescents and young adult women, and its influence on endogenous hormonal regulation through synthetic hormone administration, it is essential to examine its potential impact on mental health. Even a small increase in psychiatric risk may hold clinical significance. Therefore, the aims of this review are to assess the risk of mood disorders and depressive symptoms, including major depressive episodes, among users of oral hormonal contraception; to evaluate adolescent girls and young women as a distinct analytical subgroup; and to explore whether the type of contraceptive formulation affects the likelihood of experiencing these psychological symptoms.

Methodology

This study follows the principles of a literature review. A digital search was conducted in the PubMed database using keywords relevant to the topic: hormonal contraception, oral contraceptives, combined oral contraceptives, depression, mental disorders and mood disorders.

Evidence

Depression in Adult Women Using Hormonal Contraception

The results of available studies on the relationship between hormonal contraception use and depressive symptoms in adult women remain inconclusive and often contradictory. Some studies report a significant association between hormonal contraceptive use and increased depressive symptoms, while others do not confirm such a relationship or even suggest a protective effect.

In a large registry-based cohort study involving over one million individuals, hormonal contraceptive users were found to have a significantly higher risk of antidepressant use and depression diagnosis compared to non-users (Skovlund C. W. et al., 2016). Similar findings were reported in another study, which indicated that older contraceptive formulations—particularly those based on ethinylestradiol and androgenic

progestogens such as levonorgestrel—may be linked to mood deterioration in some women (Mu, E., & Kulkarni, J., 2022).

Conversely, a 2021 narrative review highlighted that although some women report depressive symptoms while using hormonal contraception, the data are insufficiently consistent to establish a causal relationship. The authors emphasized that reactions to hormonal contraception are highly individualized, with factors such as a prior history of depression or hormonal sensitivity influencing psychological vulnerability (Buggio L. et al., 2022).

Similar conclusions were drawn from a large cohort study of over 265,000 women, which noted an increased risk of mood disorders or depression, particularly during the first two years of OC use. This study compared pairs of sisters within a subcohort to better account for genetic and shared environmental factors. Although there was a high likelihood of both sisters using OCs (correlation = 0.2; OR = 3.08), the correlation of concurrent depression in both sisters was low (0.03) but statistically significant, supporting a potential causal effect of OC use on depression risk (Johansson T. et al., 2023).

However, a clinical trial of 69 women aged 18–35 found no significant differences in depressive symptoms between OC users and a placebo group, suggesting that OCs may not directly affect mood in healthy women (Scheuringer A. et al., 2020). Additional studies have confirmed that in women without prior depression, OC use does not increase depressive symptoms, whereas women with a history of depression may experience some symptom exacerbation, indicating the role of individual vulnerability (Morssinkhof M. W. L. et al., 2021).

In summary, the literature shows no clear consensus regarding the effect of hormonal contraception on depressive symptoms in adult women. Some studies suggest a possible association, especially with specific formulations or in women with prior mental health issues, while others—including well-designed clinical trials—do not confirm such a link. These findings underscore the need for individualized contraceptive therapy and further research considering age, psychiatric history, contraceptive type, and duration of use.

Depression in Adolescents and Young Adults Using OCs

Studies on adolescents and young adult women more frequently indicate an association between hormonal contraception and depressive symptoms compared to adult women. Several reports show that teenage OC users have a significantly higher risk of depression diagnosis and antidepressant use compared to non-users (Ciarcia, J., & Huckins, L. M., 2024).

A study of over 800,000 women demonstrated that hormonal contraceptive use was associated with an increased risk of initiating psychotropic treatment, particularly among adolescents. The strongest association was observed in girls aged 12–14 (OR = 3.46; 95% CI: 3.04–4.94), suggesting heightened susceptibility to side effects during this developmental period. No significant risk increase was observed in adult women, indicating age as a potential moderator of hormonal impact on mental health (Zettermark, S. et al., 2018).

Further evidence indicates that women who used contraception during adolescence exhibit greater emotional reactivity and vulnerability to psychological stressors in adulthood, with a higher risk of mood disorders. Compared to women who never used OCs, adolescent users had a 69% higher risk of depression; compared to women who began OC use in adulthood, the risk was 46% higher (Anderl C. et al., 2019).

A 2019 prospective cohort study found that OC use during adolescence was associated with an increased risk of depressive symptoms. Sixteen-year-old OC users more frequently experienced symptoms such as increased crying (OR = 1.89), hypersomnia (OR = 1.68), and appetite changes (OR = 1.54) than non-users. These differences remained significant after adjusting for age, socioeconomic status, and ethnicity. The authors suggested that adolescence is a particularly sensitive period of neuroendocrine development, during which exogenous hormones may affect limbic system maturation and increase vulnerability to affective disorders (de Wit A. E. et al., 2020).

Another prospective cohort study reported a small but significant increase in the risk of major depressive episodes in young adulthood following late adolescent OC use (OR = 1.41), especially in women without prior depression (OR = 1.72) (Anderl C. et al., 2021). These findings emphasize that adolescents and young women may be particularly susceptible to mood effects of exogenous hormones due to rapid hormonal changes, HPA axis maturation, and still-developing neurotransmitter systems. Responses are highly individualized, and data remain inconsistent, limiting precise risk prediction (Buggio L. et al., 2022).

However, some studies report no increased depression risk among young contraceptive users, with occasional findings suggesting a stabilizing effect on mood in specific groups (Scheuringer A. et al., 2020; Doornweerd A. M. et al., 2022).

In conclusion, while not all studies confirm a clear link between hormonal contraception and depression in young women, many—including large-scale and long-term studies—suggest an increased risk of depressive symptoms. Given the sensitivity of adolescence and potential long-term consequences, further detailed research is warranted, particularly considering contraceptive type, age at initiation, and individual biological susceptibility.

Depression and the Type and Method of Hormonal Contraception Administration

The composition and route of administration of hormonal contraception are important factors influencing its potential impact on mental health, including depressive symptoms. Several studies indicate that progestogen-only contraceptives may be more strongly associated with depression risk than combined formulations. For instance, a large Danish cohort study found that women using progestogen-based methods (e.g., minipills, implants, intrauterine systems) had a higher likelihood of developing depression than users of combined oral contraceptives. Specifically, levonorgestrel-releasing intrauterine systems (IUS) and hormonal patches were associated with increased initiation of antidepressant treatment (relative risk compared to non-hormonal contraceptive users: 1.4 for IUS, 2.0 for patches) (Skovlund C. W. et al., 2016; Mu, E., & Kulkarni, J., 2022). These findings suggest that progestogens may negatively affect serotonergic pathways and limbic structures, increasing depressive symptom risk.

Conversely, some studies suggest that combined oral contraceptives may have a neutral or even beneficial effect on mood, particularly in healthy women. A randomized double-blind placebo-controlled trial found that estradiol-based combined contraception did not significantly alter depressive symptoms or cognitive function (Scheuringer A. et al., 2020). Narrative reviews further suggest that modern formulations containing drospirenone or natural estradiol may have a more favorable psychological profile than older ethinylestradiol-based preparations with androgenic progestogens (Mu, E., & Kulkarni, J., 2022; Buggio L. et al., 2022). Mood improvement in some women after starting combined contraception may result from stabilization of sex hormone levels.

Individual psychological vulnerability and prior depression history also play critical roles. Reviews emphasize that responses to hormonal contraception are highly individualized, with women who have a history of depression at higher risk of symptom recurrence (Mu, E., & Kulkarni, J., 2022; Buggio L. et al., 2022). Conversely, in women without prior mood disorders, no significant deterioration in psychological well-being is observed, highlighting the influence of genetic, environmental, and hormonal sensitivity factors.

In summary, the type of hormonal component (progestogen vs. combined), form of estrogen (synthetic vs. natural estradiol), and route of administration (oral, transdermal, vaginal, intrauterine) influence the occurrence of depressive symptoms. Progestogen-only preparations—particularly implants and intrauterine systems—may carry higher depression risk, while modern estradiol-based combined oral contraceptives appear safer for mood. Nevertheless, these results are not conclusive and require further clinical investigation.

Discussion

The results of the reviewed studies suggest that HC use may be associated with an increased risk of depressive symptoms; however, this relationship is not unequivocal. Considerable differences between studies make it difficult to draw firm conclusions. Some studies indicate a significant association between hormonal contraception, particularly progestogen-only methods, and an increased risk of depression. Other studies do not confirm this relationship, especially among healthy women without a prior psychiatric diagnosis (Lundin C. et al., 2022).

Evidence also suggests that depression risk may be influenced by the type of hormonal preparation. Progestogen-only methods, such as implants, minipills, and intrauterine systems, appear more strongly associated with mood disorders than combined contraceptives. The type of estrogen may also be relevant; natural estradiol seems to exert a milder effect on the nervous system compared to synthetic ethinylestradiol, indicating a potential neuroprotective role of estrogen and differential effects of specific hormonal components.

Particular attention in the literature is given to adolescents and young women. In this age group, the correlation between initiation of hormonal contraception and the development of depressive symptoms appears more pronounced. Studies (Skovlund C. W. et al., 2016) suggest that exposure to exogenous hormones during adolescence may induce long-term changes in neurotransmission, brain structure, and function, potentially predisposing individuals to mood disorders later in life. These findings highlight the importance of careful consideration and psychiatric risk assessment before initiating hormonal therapy in young girls.

Despite these trends, substantial heterogeneity remains in the literature. Some studies report no statistically significant differences in depression prevalence between hormonal contraceptive users and controls. Sources of inconsistency may include study design (cohort vs. randomized), population characteristics (age, health status), follow-up duration, methods of assessing depressive symptoms (self-report vs. clinical diagnosis), and inadequate control of confounding factors (e.g., stress, socioeconomic status, mental health history).

Limitations of this narrative review include the potential for publication bias, as negative findings may be underreported. Moreover, the absence of a meta-analysis prevents quantitative assessment of effect sizes and their reliability. There is also a clear need for studies that account for individual differences in hormonal response, as well as genetic and neurobiological factors that may modulate the effects of sex hormones on mood.

Conclusions

Available evidence points to a potential link between HC use and the occurrence of depressive symptoms in women, but findings remain inconsistent. Some research, particularly large cohort studies, suggests an increased risk of depression, especially with progestogen-only formulations. Other studies, including randomized trials, do not confirm this association, particularly among healthy women using combined oral contraceptives.

Adolescents and young women initiating hormonal contraception during puberty appear to be the most susceptible to depressive symptoms. At the same time, responses are highly individualized, with some women experiencing no mood deterioration or even improved well-being. The type and method of administration also appear relevant, as progestogen-only methods may be more likely to negatively affect mood.

Further well-designed studies are needed to better identify women at risk for adverse effects and to elucidate the biological mechanisms underlying these observations.

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