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Hormonal Contraceptives and Mood: Review of the Literature and Implications for Future Research

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Abstract

Purpose of Review We examine recent studies that investigate the effects of hormonal contraception on mood in different populations of women, including women in the general population and women with diagnosed psychiatric and gynecologic disorders. We address the mechanisms of several types of hormonal contraceptives and assess how these may affect mood and gynecologic disorders.

Recent Findings The effects of hormonal contraceptives seem to be most relevant in selected subsets of women, as they may promote improved mental health in particular psychiatric disorders such as PMDD.

Summary Currently, there is no consistent evidence for negative effects of most hormonal contraceptives in the general population. Even though some studies reveal that certain individuals appear susceptible to negative mood effects from some forms of hormonal contraceptives, more research is needed to better identify these susceptible individuals.

Keywords Oral contraceptive · Mood · Depressive disorders · Anxiety disorders · PCOS

Introduction

Over the past nearly 60 years, since the invention of the combined oral contraceptive [1], these interventions have enabled global progress in family planning and unwanted pregnancies. It is estimated that over 100 million women worldwide use combined hormonal oral contraceptives [2], while many use long-acting reversible contraceptives (LARC) and intrauterine devices with locally emitted progesterone. The United Nations and World Health organizations continue to push for expansion of contraception methods since there is still a vast unmet need worldwide [3]. This international exposure of women to hormonal contraceptives has led researchers to analyze potential side effects, since sex steroids are powerful and pervasive shapers of not only the menstrual cycle but also emotions and behavior [4]. Their hormonal alteration has the potential to affect human psychology in ways not entirely foreseen. In this review, we will examine recent studies which investigate the effects of hormonal contraception on mood in different populations of women, including women in the general population and women with diagnosed psychiatric and gynecologic disorders.

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Mechanisms of Action of Hormonal Contraceptives

Hormonal contraceptives function by several cooperative mechanisms. Exogenous estrogen exerts feedback control on the follicle stimulating hormone (FSH), preventing ovulation [5] and thickening the uterine lining. Progestins not only have weaker activity in the suppression of FSH and the luteinizing hormone (LH) but also act to thicken cervical mucus and inhibit development of the uterine lining [6]. Oral contraceptives are most typically offered as combined preparations of estrogen plus progestin. They may be monophasic, providing low constant levels of both hormones, or bi- or tri-phasic, providing variable levels of estrogen and progestin over the course of a cycle [7]. There is a variety of synthetic progestins available, which differ greatly in their potency, pharmacokinetics, and pro- and anti-androgenic activity [8]. Most oral

contraceptive preparations include 3 weeks of active hormone and 1 week of placebo pills, which permit menstrual bleeding. There is no physiological purpose for the placebo week, and there are several extended cycle or continuous preparations on the market that allow for very infrequent periods [9].

Progestin-alone oral contraceptives are also available, and although they are somewhat less effective than combined oral contraceptives (COC), they avoid some of the more concerning side effects of estrogen, such as its prothrombotic properties [10] and antagonism of lactation [11]. Long-acting reversible contraceptives (LARC) are also progestin only. Some LARCs, such as depot levonorgestrel (Norplant) or depot medroxyprogesterone (Depo-Provera), depend entirely on systemic progestin activity and suppress ovulation. Intrauterine devices (IUD), such as Mirena, Liletta, Skyla, and Kyleena, combine locally emitted levonorgestrel with the contraceptive properties of the implanted intrauterine device, offering effective contraception with lower or negligible levels of systemic progestin activity [12]. Suppression of ovulation is inconsistent with hormonal IUDs. A nonhormonal IUD is also available, the copper Paragard, which does not suppress ovulation or interfere with the physiological hormonal milieu. There is also a locally acting combined contraceptive, the vaginal ring (Nuvaring), which emits estradiol and etonogestrel and is changed monthly.

Studies of Psychiatric Effects of Hormonal Contraceptives in the General Population

Contraceptive Users Vs Nonusers

There have been many epidemiological studies that use large existing datasets to explore associations of hormonal contraceptive use with mental health outcomes. There are major drawbacks to using this type of study design to investigate these questions. Chief among them is the important fact that women who use hormonal contraceptives differ in many systematic ways from women who use nonhormonal methods or no contraception. Large epidemiological databases generally offer very limited opportunities for confounder adjustment. Thus, it is very easy to discover spurious associations. Unsurprisingly, of the numerous epidemiological investigations that have been conducted, some find associations with improved mental health, others with impaired mental health, and still others report variable or conflicting results.

Toffol et al. [13] studied the effects of the levonorgestrel IUI (LNG-IUI) and OC in a nationwide, population-based Finnish sample of women (3223 women ages 18–54), reporting that use of OC was not associated with an increased risk of psychiatric diagnosis. Beck Depression Inventory scores were in fact negatively associated with the use of OC, although the findings were not significant. Similar results were found for the LNG-IUI. In a follow-up study, Toffol et al. [14] reported results from a survey of 8586 women in Finland and found systematic differences in age, education, marital status, and other factors between women using oral contraceptives vs not. Use of oral contraceptives had a slight negative association with depression as measured by BDI-13 but not BDI-21. The authors concluded that oral contraceptives were not detrimental to mental health. Keyes et al. [15] reported results from a national survey of 6654 women between ages 25–34 whose depressive symptoms were assessed with the Center for Epidemiological Studies Depression Scale (CESD). This group had robust information on covariates and found that women in different categories of contraceptive use also differed systematically in age, parity, education, exercise level, health behaviors, smoking status, and a host of other factors. Women using hormonal contraceptives reported fewer depressive symptoms and fewer past-year suicide attempts than other groups, effects that survived adjustment for the known confounders. However, given the very large and obvious systematic differences between groups in this study, it is likely that there were many other, unmeasured confounders which differed, and thus it would be premature to ascribe causality to the contraceptive method.

The nonsignificant effect of OC on mood in a general population of women is further supported by Duke et al's [16] study comparing the rate of depression symptoms in women on OC to depression symptoms in nonusers in a large cohort of women in the Australian Longitudinal Study on Women's Health. Women were surveyed for depressive symptoms with the CESD at age 22–27 years old ($N = 9688$) and 3 years later when they were 25–30 years old ($N = 9081$). No significant differences in depression symptoms were found between women taking OC and those not. However, when women took OC for non-contraceptive uses (1.05; 95% CI = 0.9–1.21), there was a difference in depressive symptoms, with higher odds of reporting depressive symptoms in women taking them for pain or other medical conditions (1.32; 95%CI 2.017–0.163). This difference between groups demonstrates the importance of clarifying the reasons women take the OC, as many women may take them for reasons other than contraception that are independent risk factors for depressive symptoms such as acne.

[17] or dysmenorrhea [18]. Since this was a cross-sectional study, it is not clear whether the depressive symptoms in these women using OC for non-contraceptive purposes actually started before the exposure to OCs.

In contrast, in a 14-year prospective study of one million women in Denmark, use of hormonal contraceptives was associated with an increased risk of subsequent treatment with antidepressants and diagnosis of depression [19]. Women ages 15–34 in the Danish National Prescription Register and the Psychiatric Central Research Register who had no prior psychiatric diagnosis and had never been prescribed antidepressants were included in the analysis. Users of hormonal contraceptives had an increased risk for first use of antidepressant compared with nonusers.

The greatest increased risk for first antidepressant used and depression diagnosis occurred in adolescents aged 15–19 years old and in patients starting antidepressants within 1 year of oral contraceptive initiation. The study did not control for important variables that may have contributed to greater risk for depression in the hormonal contraceptive group, such as possible increased psychosocial and interpersonal stress in adolescents initiating sexual activity or detection bias.

In a follow-up study, Skovlund and colleagues [20] reported that hormonal contraception use was positively associated with subsequent suicide attempt and suicide, and adolescent women experienced the highest relative risk. In this study, former contraceptive use was found to be associated with an even higher hazard ratio than current contraceptive use, highlighting the likelihood that confounding was a more likely explanation than a direct biological effect of hormone exposure.

Age was also found to be an important determinant of hormonal contraceptive mood effects in a study of 815,662 Swedish women with no previous history of psychiatric diagnosis. All women ages 12–30 years old were followed from the time they were given a prescription for hormonal contraception to either a prescription fill for antidepressants or completion of a one-year follow-up. While an association between HC and psychotropic drugs (adjusted OR 1.34, 95% confidence interval (CI) 1.30–1.37) was found for the group as a whole, when the analysis was age stratified, a stronger association was found in adolescent girls (adjusted OR 3.46, 95% CI 3.04–4.94 for age 12 to 14 years). Women aged 20–30 showed no association [21].

Because much of the data available regarding mood changes in women exposed hormonal contraceptives comes from epidemiological surveys and because pre-existing mental health factors have been repeatedly shown to affect choice of contraceptive [22–25], confounding is an important factor to keep in mind. Randomized trials are necessarily smaller but provide higher quality information. An important randomized prospective trial of COC effects on mood with daily rating scores found variation in different phases in the cycle, but no significant overall mood changes for the majority of women [26••]. This group did identify a subgroup of women with higher susceptibility to mood disruption by COC, an important concept for the clinician that is difficult to elicit from epidemiological survey data.

Future studies of the effects of hormonal contraceptives on mood should compare individual contraceptive interventions in homogenous age groups, as well as specific depression and anxiety subtype groups in randomized placebo-controlled studies. The observed negative effects of hormonal contraceptives found in studies may be due to uncontrolled factors such as greater psychosocial stress, family history of depression or comorbid medical or substance abuse problems between the groups, or due to differential effects of hormonal preparations on the central nervous system. This issue of confounding may explain why some of the large observational studies [19, 20] report adverse mood effects of hormonal contraceptives, while randomized controlled trials typically do not find clinically significant effects of oral contraceptives on mood [27, 28].

Effect of Hormonal Contraceptives on Mood in Specific Gynecologic and Psychiatric Populations

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder characterized by hyperandrogenemia, irregular menses, and polycystic ovaries and typically associated with insulin resistance and reduced fertility [29]. PCOS is also associated with increased risk for depression [30].

Hormonal contraceptives are a first-line treatment for PCOS; they help reduce the hyperandrogenemia and prevent endometrial hyperplasia associated with irregular ovulation [31, 32]. Information on the effect of OCP on depression in women with PCOS is scant. One observational study reported that depression was lower in women with PCOS who were also treated with OCP [33], while another reported no benefit for mood in women with PCOS after initiation of OCP [34]. As with other populations, the likelihood that an individual with PCOS and depression will see psychiatric benefit from OCP may be related to a number of other factors, including the individual's unique response profile to exogenous gonadal steroids and the specific progestin and dosing regimen in the chosen preparation. Further study is needed to determine whether and under what conditions OCP is beneficial for mood in women with PCOS.

There is only one psychiatric disorder for which hormonal contraceptives have established benefit—premenstrual dysphoric disorder (PMDD). Hormonal contraceptives have been hypothesized to provide benefits for women with several other types of psychiatric conditions, as well, but these are less clearly established.

Premenstrual Dysphoric Disorder

PMDD involves recurring destabilization of mood during the latter part of the luteal phase of the menstrual cycle, just prior to menses. In this phase, estrogen and progesterone both initially increase rapidly, then decline to their minimum monthly concentration. They will remain at this level until the cessation of menses, when estrogen commences a slow rise, nurturing the maturation of the next cycle's ovum.

Sufferers of PMDD do not differ from healthy controls in their serum concentrations of gonadal steroids [35]; rather they react poorly to abrupt alterations in these concentrations [36, 37••]. The underlying deficit may be related to differences in estrogen effector complexes at the cellular level [38••].

Women with PMDD generally find relief when the constant flux of hormones that characterizes the physiological menstrual cycle is changed to a steady state, as with use of COCs.

Suppression of ovulation with hormonal contraception is often effective for PMDD, although placebo responses are also high, which complicates assessments of efficacy [39]. Given the sensitivity of PMDD sufferers to temporal fluctuation in hormone levels, bi- and tri-phasic oral preparations are best avoided. Continuous preparations have shown reasonable efficacy against placebo for PMDD [39], although the one existing head-to-head trial that compared continuous with intermittent dosing found no separation from placebo for either regimen [40•]. The anti-androgenic progestin drospirenone has been hypothesized to be specifically beneficial for PMDD, and COC with this progestin has demonstrated efficacy against placebo [41, 42]. Head-to-head comparisons with other hormonal preparations have not been conducted. Locally acting contraceptives that do not reliably suppress ovulation are not likely to be effective for PMDD, and thus have not been specifically studied for this indication.

Bipolar Disorder

Women with bipolar disorder who are concurrently using oral contraception may experience a less severe course of disease than women using nonhormonal methods or no contraception [43]. In a study of 17 women with bipolar disorder who were prospectively studied with ChronoRecord, an online symptom charting method, Rasgon et al. [33] reported that women taking OCs did not report changes in mood symptoms across the menstrual cycle, while women not on OCs did.

Bipolar disorder in women sometimes presents with menstrual entrainment i.e., mood cycling that is linked to the menstrual cycle [44, 45]. It remains a matter of debate whether this phenomenon should be classified as a specifier to bipolar disorder or as comorbidity of bipolar disorder with PMDD. Bipolar disorder with menstrual entrainment can be quite difficult to differentiate from nonbipolar premenstrual dysphoric disorder (PMDD) in clinical practice. The diagnostic criteria for PMDD comprise five or more psychiatric and physical symptoms (at least one must be characteristic mood symptoms or depressed mood, irritability) during the luteal phase only of the menstrual cycle with remission within a few days of onset of menstrual flow for most menstrual cycles [46]. The distinction relies on whether manic or hypomanic episodes have ever been observed, as PMDD does not present with classic euphoric mood elevation. Historical hypomanias that presented with moderately increased energy and productivity are rarely identified as pathological by the patient and can be missed in even a careful history. When irritability is the predominant symptom of hypomania, it can be misdiagnosed as PMDD.

The distinction between PMDD and menstrually entrained bipolar disorder is important, as it will affect treatment decisions [47]. PMDD, especially the hallmark symptoms of anger and irritability, is often effectively treated with luteal-phase antidepressants [48, 49•], whereas in most cases of bipolar disorder, antidepressants should not be prescribed without a concurrent mood stabilizer, due to the risk of precipitating mania [50, 51]. Hormonal contraceptives, however, may play important roles for both populations.

At present, there are no clinical trials of hormonal contraceptive treatment for menstrually entrained mood cycling in women with bipolar disorder or in women with comorbid PMDD. Slyepchenko et al. [52] reported that women in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) reported more mood symptoms with oral contraceptives than women without comorbid PMDD on OCPs. Notably, however, this was a post hoc analysis and the premenstrual symptoms were not prospectively charted. Further prospective research is needed to identify the factors that determine whether hormonal contraceptives affect mood in this population. OCPs have been shown to reduce the effective serum levels of both valproate and lamotrigine [53]. Conversely, carbamazepine, oxcarbazepine, and topiramate have been shown to induce cytochrome P450 3A4, leading to enhanced metabolism of either or both the estrogenic and progestogenic components of OCPs and thus reducing their effectiveness [54, 55]. In contrast to the pharmacometabolic concerns, there are some preliminary indications that lamotrigine may act synergistically with OCP to both lift and stabilize mood fluctuations over the menstrual cycle [56], though this hypothesis requires further study.

Current Major Depression in Premenopausal Women

While many women with depression also report premenstrual mood irregularities [57], there are no interventional studies of hormonal contraceptive as a primary treatment for mood disorders. There is a post hoc analysis of citalopram intervention using a subpopulation from the STAR*D trial, (Sequenced Treatment Alternatives to Relieve Major Depression) which found that women who were taking OCP at baseline were more responsive to citalopram in unadjusted, but not adjusted, analyses [58]. An observational analysis of the same population at baseline compared women taking COC with women using progestin-only or nonhormonal contraceptives [59]. Some differences in hypersomnia, weight gain, sexual interest, and gastrointestinal upset emerged, and women taking COC had significantly fewer obsessive–compulsive symptoms than women in either of the other two groups. However, no mood symptoms survived adjustment for confounders. In this study, women on combined preparations were more likely to be Caucasian, more likely to be employed, and more likely to be privately insured than women on progestin-only or nonhormonal contraceptives, and thus likely differed in a multitude of other ways that were not directly

related to their contraceptive choices. Pagano et al. [43] reviewed cohort, randomized control and case control studies of women with clinically diagnosed depressive or bipolar mood disorders exposed to hormonal contraception. They identified six studies that investigated whether hormonal contraceptive affected mood in women who were being treated for their mood disorder with either antidepressants or mood stabilizers. COC or OC use was not associated with increased depressive symptoms or increased rates of psychiatric hospitalization.

Thus, the available data suggest neither a negative effect nor a specific benefit of COC for major depression in premenopausal women. The data suggests that confounding socioeconomic variables are important to keep in mind when exploring associations between contraceptive use and mood symptoms, and more well-controlled studies are recommended of the effects of hormonal contraceptives in premenopausal women with unipolar or bipolar depression. Furthermore, unlike with mood stabilizers, there has been very limited research regarding the effect of OCPs on antidepressants. In the only systematic review published to date of the interaction of OCPs and serotonin reuptake inhibitors ($N = 5$), tricyclic antidepressants ($N = 4$), bupropion ($N = 1$), atypical antipsychotics ($N = 3$), and benzodiazepines (N = 5), no studies reported decreased efficacy of medication on psychiatric symptoms when combined with a hormonal contraceptive [60]. More studies are needed of individual hormonal contraceptive preparations and individual antidepressants in order to better understand how OCPs affect psychotropic pharmacokinetics.

Major Depression with Premenstrual Exacerbation

Premenstrual worsening of major depression is common in women, and a post hoc analysis of the STAR-D trial reported a rate of 66% [61]. An earlier open-label study reported that OCPs (estradiol/drospirenone) improved premenstrual breakthrough of depression [62]. However, in the only randomized placebo-controlled study to date of women with MDD in remission on a stable dose of antidepressant with MDPE, there was no significant difference between treatment with drospirenone/estradiol OCP or placebo for 2 months, and both groups showed improvement of premenstrual depressive symptoms. This study was small ($N = 25$) and relatively short in duration, and future studies with larger sample sizes and longer duration are needed to further clarify the role of OCPs in improving MDPE.

Perimenopausal Depression

A recently published guideline for the evaluation and treatment of perimenopausal depression by the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers (NNDC) reported that while traditional estrogen replacement therapy (ERT) has been shown to be an adjunctive treatment to antidepressants for perimenopausal depression, the mood effects of combined oral contraceptives have not been specifically studied in this depression subgroup [63]. To date, no studies have specifically investigated the effects of hormonal contraceptives on mood symptoms in perimenopausal women; however, given their beneficial effects on vasomotor symptoms and menorrhagia and improved mood effects at higher standard ERT doses, they may be found to be either mood neutral or beneficial in this group.

Anxiety Disorders

Regarding obsessive–compulsive disorder (OCD), while the result from Young et al. is intriguing, and there are data to suggest roles for sex steroids in OCD [64–67], investigations of women with diagnosed OCD taking hormonal contraceptives find that most women do not report any effect of OCP on their OCD symptoms, and the minority who do are split between improvement and worsening [68, 69]. Despite these studies suggesting possible effects of hormonal contraceptives on anxiety disorders, there have not been any controlled prospective studies examining this connection.

Postpartum Patients

Contraceptive use postpartum is recommended in order to decrease the risk of unintended pregnancies [2]. Progesterone-only contraceptives rather than combined progesterone and estrogen preparations are recommended in the early postpartum period of up to 42 days; controversy remains regarding the use of estrogen containing pills in women who are breastfeeding [70]. Very few studies have investigated the effects of hormonal contraceptives on mood in postpartum women. One double-blind placebo-controlled RCT of 180 women found that long-acting progestogen contraceptive given within the first 48 h of birth compared with placebo injection was associated with an increased risk of depressive symptoms as measured by the EPDS at 6 weeks postpartum (EDPS > 11; relative risk 1.75, 1.12 to 2.72)[59]. In a study of records of 75,528 women in the US military medical insurance system, rates of diagnosis of major depression and antidepressant prescription during the first year postpartum were compared between hormonal contraceptive users and nonusers (they excluded women who had been diagnosed with major depression or used antidepressants in the 2 years prior to pregnancy to rule out ongoing perinatal depression). After controlling for demographic factors, norethindrone-only pills were associated with an increased risk of antidepressant use, but a decreased risk of depression diagnosis. The ethinyl estradiol/etonogestrel ring was also associated with a higher risk of antidepressant use, but no significant change in risk for

depression diagnosis. None of the other forms of hormonal contraceptives used (ethinyl estradiol/norethindrone or ethinyl estradiol/norgestimate pills and etonogestrel subdermal implant). The levonorgestrel intrauterine system was in fact associated with decreased risk of depression diagnosis [71]. Since the postpartum period is a unique hormonal milieu, especially in women who are breastfeeding, and postpartum depression is a prevalent condition with significant morbidity and potential mortality, further studies are needed to clarify whether estrogen or progesterone containing hormonal contraceptives have differential effects in the postpartum.

Suggested Mechanisms for Observed Effects

Many studies have shown that gonadal hormones exert both structural and functional effects on the human brain. Estrogen receptors are found in areas that are involved in emotion regulation such as the amygdala and the hypothalamus, and animal studies have demonstrated that both estrogen and progesterone modulate synthesis of neurotransmitters associated with mood, such as serotonin [72]. While synthetic progestins vary greatly in their biological activity, many of them are known to cross the blood-brain barrier after oral administration and to have a plethora of effects on CNS targets of progesterone [73].

Consequently, different preparations of hormonal contraceptives containing differing amounts, types, and ratios of estrogen and progestin may exert differential central nervous system effects. Observational studies suggest that a minority of women may be especially sensitive to these effects and recent functional neuroimaging studies further support this. For instance, in a placebo-controlled study of women with a previous history of adverse psychiatric side effects on COCs, mood deterioration recurred when exposed to an oral contraceptive containing 30 μg ethinylestradiol and 0.15 mg of levonorgestrel but not when exposed to the placebo. fMRI differences were also found between the placebo and COC groups—COC users had lower emotion-induced reactivity in brain areas associated with emotion regulation and recognition, the left middle frontal gyrus and bilateral inferior frontal gyri [74].

For comparison, a prospective structural and functional MRI study of healthy young women before and after initiation of oral contraceptives reported an association of reduced gray matter volume in the amygdala and parahippocampal gyrus with reductions in positive affect in the COC group, and also noted relative changes in functional connectivity between the amygdala and the dorsolateral prefrontal cortex between the COC and comparison groups [75]. The frontal gyri were not implicated in this work.

Other investigators have found reductions in amygdalar reactivity [76] and blunted responses to stress tests [77] in users of COC. This and related work has been interpreted to suggesting that COC promote an affective blunting [78] that could be perceived as either stabilizing or disagreeable, depending on the individual's history and perspective.

In contrast, LNG-IUD may prompt increased sensitivity of the of the hypothalamic-pituitary adrenal (HPA) axis responsivity, negatively influencing mood and emotion. Women using LNG-IUD have significantly increased cortisol and heart rate responses when moderately stressed compared with oral estrogen–progestin contraception or natural menstrual cycling [79].

At present, the available data that speak to neurophysiological explanations for the observed effects of hormonal contraceptives on mood are sparse, but could suggest that affective blunting induced by hormonal contraceptives could be an important mediator of observed effects on mood.

Conclusion

Hormonal contraceptives are widely used and contain both estrogen, a compound that crosses the blood-brain barrier and subserves important functions in the brain and a variety of synthetic progestins, many of which cross the blood-brain barrier and have a variety of effects on CNS receptors for progesterone. Thus, effects of these preparations on mood and cognition are to be anticipated.

Overall, however, the effects of hormonal contraceptives on mood appear to be most relevant in selected subsets of women. They may promote improved mental health in particular psychiatric disorders such as PMDD. Conversely, certain individuals appear susceptible to negative mood effects from some types of hormonal contraceptive; however, in practice, this is difficult to predict, and more research is needed to define the physiological causes and to better identify susceptible individuals.

At present, there is no consistent evidence for negative effects of most forms of hormonal contraceptive in the general population. Epidemiological studies have shown varied and conflicting results, most likely related to unmeasured confounding factors. In contrast, the personal control over fertility as well as management of numerous steroid-responsive disorders that these medications provide are of clear and important value in promoting women's physical and mental health and social well-being.

While individual women who have experienced adverse psychiatric reactions to hormonal preparations do well to be cautious, we do not believe that increased psychiatric surveillance at a population level is necessary for users of these widely used and important medications.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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