Current Obstetrics and Gynecology Reports (2020) 9:112–119
https://doi.org/10.1007/s13669-020-00295-9

FAMILY PLANNING (A BURKE, SECTION EDITOR)

Effects of Hormonal Contraception on Mood

Andrea Hsu Roe[1] · Priya Kumar-Kaparaboyna[2] · Margo Nathan[2] · Caryn Dutton[3]

Published online: 6 July 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Purpose of Review This review will clarify the complex relationship of hormonal contraception and mood in women both with and without mood disorders, in adolescents, and in postpartum women.

Recent Findings Though the overall effect of hormonal contraception on mood does not appear to have a significant clinical impact, several recent population-based studies suggest adolescents are potentially more vulnerable than adults.

Summary Strategic initiation of hormonal contraception may mitigate mood symptoms, with continuous regimens of hormonal therapy demonstrating some benefit over cyclic regimens. Additional rigorous studies are needed to measure the impact of hormonal contraception on mood relative to dose and formulation, particularly in those women with pre-existing mood disorders.

Keywords Hormonal contraception · Mood disorder · Adolescents · Premenstrual dysphoric disorder

Introduction

The relative risk of experiencing a major depressive episode is known to be higher in females compared with males, and the disparity in prevalence develops with transition to adolescence [1]. However, the mechanisms for this sex difference are not fully understood. A majority of women also report changes in mood associated with menses [2]. Understandably, both patients and health care providers may be wary of initiating hormonal therapy, for fear of triggering or aggravating mood symptoms. Fortunately, studies suggest that prescription of hormonal contraception likely has minimal clinical effect on mood and in some cases may be beneficial for stabilizing mood. This article will review the evidence for any effect of hormonal contraception in women both with and without mood disorders, in adolescents, and in postpartum women. In addition, we describe the use of hormonal contraception to treat peri-menstrual changes in mood and an approach to mitigating mood symptoms when initiating hormonal contraception.

This article is part of the Topical Collection on *Family Planning*

✉ Caryn Dutton
cdutton@bidmc.harvard.edu

Andrea Hsu Roe
andrea.roe@uphs.upenn.edu

Priya Kumar-Kaparaboyna
pkumar-kaparaboyna@bwh.harvard.edu

Margo Nathan
mdnathan@bwh.harvard.edu

[1] Department of Obstetrics and Gynecology, University of Pennsylvania Health System, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

[2] Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[3] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA

Pathophysiologic Basis for a Relationship Between Hormonal Contraception and Mood

Hormonal contraception may impact mood; however, the pathophysiologic basis for this is not fully known. Several potential mechanisms may underlie this association. One theory is that a subset of women are differentially sensitive to fluctuations in female sex hormones [3]. For example, a study of women with a history of premenstrual mood symptoms showed that these women have normal physiologic levels of female reproductive hormones that are comparable with women without premenstrual mood symptoms [4]. For women with premenstrual mood symptoms, leuprolide treatment resolves their symptoms, and subsequent addition of female gonadal steroids (estradiol or progesterone) makes these symptoms recur; however, women without premenstrual

mood symptoms do not exhibit the same response to these hormones, suggesting that it may be fluctuations in levels, and not absolute levels of these hormones, that correlate with mood symptoms [5]. The reasons why some women are more sensitive to physiological hormonal fluctuations than others are not yet fully understood.

At the neurobiological level, female sex hormones are known to act on both neurotransmitter pathways and brain regions involved in mood regulation. Prior studies have demonstrated that progesterone metabolites modulate the GABA-A receptor complex [6], which has been identified in mouse model studies as a component of the pathophysiology underlying perinatal depression [7]. In human studies, lower levels of allopregnanolone, an endogenous metabolite of progesterone, have been found in women who develop perinatal depression [8]. Greater levels of progesterone metabolites have been found during the luteal phase of the menstrual cycle [6], which is the cycle phase associated with greatest risk for mood symptoms. Exogenously administered progestins are also known to increase levels of monoamine oxidase, an enzyme that degrades serotonin and therefore may contribute to increased depression and anxiety symptoms [9]. Studies following women across reproductive transitions have shown that exposure to variability in estradiol is linked with the onset of mood symptoms, rather than the absence of this hormone [10, 11]. Supporting this theory, women with a quicker transition to menopause often experience fewer depressive symptoms compared with women who experience a longer transition [12]. There is also some limited evidence that estrogen may increase serotonin synthesis and decrease its degradation [10, 13]. In addition to the effects of female gonadal hormones on neurotransmitter pathways, neuroimaging studies have shown increased activity with both endogenous cycling and exogenous exposure to female sex hormones in regions of the brain involved in emotional processing [14].

Effects of Hormonal Contraception on Mood in Healthy Adults

Depressive symptoms were commonly reported by women in the era after oral contraceptives were first approved. For example, a 1968 study documented that 44% of women on one type of COC experienced depression and loss of libido [15]. However, COCs studied at that time and even up to the 1980s included higher doses of ethinyl estradiol and progestin formulations than are prescribed today. Presently, although one-quarter of women self-report adverse mood changes with modern pill formulations [16], only 5% will discontinue the pill for this reason [17].

On a general population level, there is conflicting evidence regarding the impact of hormonal contraception on the incidence of depression, although the absolute risks appear to be low. In a longitudinal study of 6654 sexually active women in the USA, those using the progestin implant Norplant, depot medroxyprogesterone injection, and the COC, patch, and ring, were compared with users of barrier or withdrawal methods or no contraception [18]. Users of all combined methods of hormonal contraception had lower mean depressive symptoms scores on the Center for Epidemiologic Studies Depression Scale (5.6 vs 6.9 and 7.3, a total of 30 points) and were less likely to have a high level of depressive symptoms, defined as CES-D $\geq$ 11 points (OR 0.68, 95% CI 0.49, 0.94, compared with users of no hormonal contraception) even after adjustment for demographic variables and controlling for previous high depression scores. Women who used hormonal contraception were also less likely than those who used no contraception to report a suicide attempt in the previous year (OR 0.37, 95% CI 0.14, 0.95). Among the 298 total women in this cohort using the progestin implant or injection, no differences in depressive symptoms were seen compared with users of other forms of hormonal contraception.

In contrast, among a Danish registry study of over one million women, those who initiated combined oral contraception were more likely to subsequently start an antidepressant (rate ratio (RR) 1.2, 95% CI 1.22, 1.25), be diagnosed with depression for the first time (RR 1.1, 95% CI 1.08, 1.14), or attempt suicide (relative risk 1.97, 95% CI 1.85, 2.10) compared with women who never used or formerly used hormonal contraceptives [19, 20]. The incidence of antidepressant initiation was 2.2 per 100 woman-years in users of all hormonal contraception, compared with 1.7 per 100 woman-years in non-users. For suicide attempts and completed suicide, the increase in incidence was 3/10,000 person-years and 14/100,000 person-years, respectively. Thus, while these two large studies show conflicting outcomes, in neither does hormonal contraception appear to appreciably impact the incidence of depression or suicide on an absolute scale.

In recent double-blind randomized controlled trial, 202 healthy women were randomized to either a COC or placebo for three cycles [21••]. The COC worsened anxiety, irritability, and mood swings during the intermenstrual period (defined as cycle day 5–21), but improved depression symptoms during the premenstrual period, as measured by the Daily Record of Severity of Problems (DRSP.) Although statistically significant, all of these mean differences were small (less than 0.4 points along a 6-point Likert scale for each measure) and the clinical significance of these effects is therefore less clear. The COC and placebo groups did not differ in new-onset subclinical depression (9.6% COC vs 6.4% placebo, $p = 0.423$).

Studies examining other hormonal contraceptive methods likewise suggest a lack of association with mood effects among healthy users. One randomized controlled trial comparing progestin-only pills with COCs showed that progestin-only pills compared favorably to both combined pills and placebo on daily ratings of mood (5-point scale) and the

Beck Depression Inventory; these effects were statistically significant but small [22]. Prospective studies of depot medroxyprogesterone acetate injection and the levonorgestrel intrauterine device (IUD) in healthy women demonstrate no adverse effect on depression risk [16, 23, 24]. However, non-randomized studies suffer from potential confounding, including the fact that current and past depressive symptoms may be associated with choice of contraception [25] and with discontinuation of contraception [26]. Unfortunately, randomized controlled trials examining the mood effects of hormonal methods, other than the ones described above, are lacking. Nevertheless, the current evidence points toward a minimal, if any, effect of hormonal contraception on development of depressed mood in healthy women.

Effect of Hormonal Contraception on Mood in Adolescents

Age may modify the effect of hormonal contraception on mood, with adolescents being potentially more vulnerable than adults. A population-based study followed over 800,000 Swedish women ages 12 to 30 years with no psychiatric history and compared initiation of psychiatric medication among users and non-users of hormonal contraception over 1 year of follow-up [27]. Overall, there was an association between hormonal contraception and psychiatric medication (aOR 1.34, 95% CI 1.30–1.37), but an age-stratified analysis demonstrated that the strongest association was among adolescent girls ages 12 to 14 (aOR 3.46, 95% CI 3.04–4.94) with no association for women ages 20 to 30.

Findings from a Danish cohort study support the association between depressive symptoms and COC use among adolescents [28]. Among 1000 adolescent females from age 16 to 25 who were assessed at four time points, there was no overall relationship between scores and COC use on the DSM-IV-oriented self-reported affective problems scale (mean item score range 0–1, with > 1 corresponding to criteria for major depressive disorder). However, COC users at the earliest time point (age 16) reported higher depressive symptoms scores (mean score 0.40 vs 0.33, $p < 0.001$), even after adjustment for age, socioeconomic status, and ethnicity. Adjusting for the existence of depressive symptoms prior to COC use weakened, but did not eliminate this association, suggesting a possible bidirectional relationship between COC use and depressive symptoms among adolescents.

In contrast, a double-blind randomized controlled trial of 76 adolescent girls younger than age 20 initiating a COC or placebo measured side effects, including depressive symptoms according to the Center for Epidemiologic Studies Depression Scale (CES-D, score range 0–60, with 16 or greater signaling risk of depression) [29]. Mean CES-D scores were the same across groups at baseline and after 3 months [14.0 in the COC group, 14.4 in the placebo group, $p = 0.86$], and decreased slightly but significantly over the study period. Self-reported mood swings occurred in one-quarter (COC group) to one-third (placebo group) participants but this difference was not statistically significant.

As with the literature on adult women, randomized controlled trials of hormonal contraception and mood are scarce, and therefore potential confounding remains a weakness of these research studies. However, other than the large cohort study above that demonstrated an age effect, non-randomized studies of adolescents have largely shown no association between hormonal contraception and depressive symptoms and disorders. In a prospective study of over 1700 young women under age 25 who initiated combined oral contraceptives, a minority reported an increase or decrease in moodiness, but most women reported no change in mood symptoms [16]. Other negative studies include a cross-sectional study of nearly 5000 female adolescents ages 13 to 18 which assessed oral contraceptive use and history of depression via interview [30] and a 3-month prospective study of 193 adolescents ages 14 to 20 initiating any form of hormonal contraception and measuring health-related quality of life and mood subscales [31].

Effect of Hormonal Contraception on Women with Mood Disorders

Women with underlying mood disorders, such as major depressive disorder (MDD) or bipolar disorder, may exhibit premenstrual worsening of their symptoms. For these women, there are several approaches to treatment. Optimizing the primary psychiatric treatment with antidepressants or mood stabilizers to address these symptoms is the most established treatment practice. However, use of hormonal contraception may stabilize variable hormone levels and treat the premenstrual component of their symptoms [3].

A small number of studies have evaluated the impact of hormonal contraception on mood symptoms in women with underlying affective disorders. In premenopausal women with MDD, available studies have shown variable results as to whether depressive symptoms worsen or improve in relation to use of hormonal contraception [32]. Pagano et al. reviewed six studies of hormonal contraception in women with MDD and did not find any significant increase in affective symptoms [33•]. Limited research on adding hormonal contraception in women already using antidepressant treatments has demonstrated minimal to no improvement in mood symptoms [34, 35]. The methodology of these studies, however, makes it difficult to draw definitive conclusions about the impact of hormonal contraception on affective symptoms in women with MDD. Specifically, these studies are largely retrospective, included women with a range of illness severities, evaluated women with hormonal sensitivity and women without

hormonal sensitivity together, and often did not differentiate between the types of hormonal contraception used.

Limited research exists on hormonal contraception for treatment of perimenopausal depression. However, there are other benefits to the use of certain kinds of hormonal contraception during perimenopause (such as improving vasomotor symptoms) which separately are linked to depressive symptoms and may improve depressive symptoms [36]. Future research is needed to systematically examine the impact of hormonal contraception on depression in midlife.

Regarding bipolar disorder, studies evaluating the impact of hormonal contraception on mood symptoms in this population have been variable. Some studies suggested that women with bipolar disorder may experience less mood symptoms across the menstrual cycle when taking hormonal contraception [37]; however, others showed no substantial impact of hormonal contraception on mood in this population [32]. Most of these studies do not examine mood symptoms prospectively, include a range of hormonal contraceptives, do not distinguish between women with a history of reproductive related affective symptoms and those without, and do not distinguish between bipolar I versus type II disorder. Given the heterogeneity in these studies and lack of prospective data, it is difficult to draw conclusions about the impact of hormonal contraception on mood in this population.

Hormonal Contraception to Treat Premenstrual Dysphoric Disorder

Up to 85% of women describe one or more mild premenstrual mood and/or somatic symptoms, 20–25% report moderate to severe symptoms, and 5% of reproductive-aged women have symptoms that meet diagnostic criteria for the most severe form, premenstrual dysphoric disorder (PMDD), as defined by the Diagnostic and Statistical Manual for Mental Disorders [2, 38]. A diagnosis of PMDD requires a minimum of five symptoms in the week prior to onset of menses during most cycles, with improvement at onset of menses and resolution in the week after menses. The symptoms should result in clinically significant distress or functional impairment and must include one core mood symptom (marked affective lability, depressed mood, or anxiety), in addition to physical or behavioral symptoms such as decreased interest in activities, disruption in sleep/appetite, low energy and others [38]. The etiology of PMDD is likely multifactorial; however, multiple theories suggest women with PMDD may have alterations in neurotransmitters or neuroreceptors due to a heightened or differential sensitivity to estrogen and especially to the neurosteroid allopregnanolone, a metabolite of progesterone [2, 39•].

While selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for PMDD, a second strategy is to offer hormonal contraception to suppress ovulation and therefore minimize peri-menstrual symptoms [2]. Studies of a COC (ethinyl estradiol 20 mcg and drosperinone 3 mg) that effectively reduced premenstrual emotional and physical symptoms as measured by scores on the DRSP prospectively compared with placebo resulted in FDA approval of this formulation for treatment of PMDD [40, 41]. While the effect on physical and mood symptoms was demonstrated to be superior to placebo at up to 3 months of use, the placebo also had a large effect, other hormonal contraceptives may be effective, and long-term studies of benefit for controlling symptoms of PMDD are needed [42].

For women without mood disorders taking COCs, the traditional premenstrual symptoms of breast tenderness, cramping, headache, and others are more prevalent during the hormone-free interval compared with other times in the cycle [43]. Thus a decrease in the length of the hormone-free interval, or extended cycle use (with menses every 3 months) or continuous hormone use (to skip menses), are all likely to further reduce pre-/peri-menstrual symptoms. When continuous use was studied for women with PMDD, significantly more subjects randomized to continuous levonorgestrel-containing COCs reported a decrease in scores representing depressive and physical symptoms compared with placebo after 4 months [44]. Though placebo response is noted to be high in all PMDD trials, the authors note that the regimen was safe and effective in decreasing symptoms of PMDD. For women complaining of peri-menstrual symptoms who are already taking COCs, we recommend they adjust their pill schedule to reduce or eliminate hormone-free intervals to minimize the frequency of menses. Similar benefit would be expected with extended cycle or continuous use of the contraceptive ring or patch though no studies are available. For women initiating COCs to treat symptoms of PMDD, use of drospirenone-based pills may be effective, though the benefit compared with other types of progestins is unknown [42].

Does Use of Hormonal Contraception Increase Risk of Depression in Postpartum Women?

Up to 19% of women report postpartum depressive symptoms, and as many as 7% of women will meet criteria for a MDD in the first 3 months postpartum [45]. Because these symptoms are so common and can have significant consequences for both maternal and newborn health, it is important to address any concerns about the impact of contraceptive method selection on mood. Unfortunately, there are very few high-quality studies reporting the impact of contraceptive use on development of postpartum depression using validated measures [46••].

A recent systematic review concluded there are no consistent associations between use of hormonal contraception and

the development of postpartum depression compared with women on non-hormonal or no contraception [46••]. Included was an analysis of military insurance data from over 75,000 postpartum women with conflicting results, finding an increased risk of prescription of antidepressants with use of the contraceptive implant (HR 1.22, 95%CI 1.06–1.41) and the contraceptive ring (HR 1.45, 95%CI 1.16–1.80), but a decreased risk of antidepressant prescription with norethindrone-only pills (HR 0.58, 95%CI 0.52–0.64) compared with women not using hormonal contraception. A diagnosis of depression was less likely in postpartum women using the levonorgestrel IUD (HR 0.65, 95%CI 0.52–0.82) or norethindrone-only pills (HR 0.56 95% CI 0.49–0.64). Use of COCs was not associated with either prescription of an antidepressant or a diagnosis of depression in the postpartum period [47]. Unidentified confounding variables may explain why COCs had no effect while use of a contraceptive vaginal ring, with lower systemic levels of hormones, was found to have a stronger association with postpartum prescription of an antidepressant. The authors suggest that the relationship between etonogestrel-based methods (both the implant and ring) and postpartum depression should be further evaluated, as well as the potential protective effect of the levonorgestrel IUD and norethindrone-only pills [47].

Because estrogen use is not recommended in the immediate postpartum period due to increased risk of venous thromboembolism, women initiating hormonal contraception are advised to use a progestin-only method, including the implant, pills, injection, or IUD [46••]. A systematic review of progestin-only contraceptive methods concluded that despite provider "perception" of impact, studies have not supported a consistent association with the development of postpartum depression [48]. Also, there was no association between use of any contraceptive method and postpartum depressive symptoms reported using 2009–2011 Pregnancy Risk Assessment Monitoring System (PRAMS) data that included over 16,000 women [49]. In the absence of a consistent association, appropriate hormonal contraception can be offered to postpartum women without concern for increased risk of depressive symptoms.

Potential Interactions Between Hormonal Contraception and Medications to Treat Mood Disorders

Pharmacokinetic studies of interactions between hormonal contraceptives and psychotropic medications are limited. In general, there is no concern for a clinically significant impact on treatment outcomes for mood disorders with concomitant use of oral hormonal contraception [50]. There are no pharmacokinetic studies evaluating interactions between psychiatric agents and non-oral hormonal contraceptives (including the ring, patch, DMPA, the implant, or IUDs). Limited reports related to tricyclic antidepressants suggest a concern for increased levels of amitriptyline and imipramine with hormonal contraceptive use, therefore patients should be monitored closely by their prescribing clinicians [51].

Some women may be prescribed medications to treat mood disorders that are potent inducers of the CYP450 enzymes in the liver. (e.g., carbamazepine, oxcarbazepine) These specific enzyme-inducing medications lower serum levels of contraceptive hormones and can result in contraceptive failure [51]. IUDs or permanent contraception (sterilization) can provide an effective alternative for these patients as they are not susceptible to this interaction. If after counseling regarding the potential interaction women choose to use oral contraceptives in addition to enzyme-inducing medications, additional use of condoms is recommended. When lamotrigine (LTG) is used as a mood stabilizer, initiation of estrogen-containing hormonal contraception can lower LTG levels by 41–64% [51]. While this is not a contraindication, dose adjustment of LTG should be coordinated with a psychiatrist familiar with this interaction, both at initiation of hormonal contraception and in the event of discontinuation. LTG toxicity is a potential risk in the hormone-free interval of cyclic oral contraceptives, therefore continuous dosing of hormones should be considered. There are no reports of a clinically significant interaction between LTG and progestins, therefore initiation of a progestin-only contraceptive does not require the same need for dose adjustment and monitoring.

Strategic Prescription of Hormonal Contraceptives May Mitigate Mood Symptoms

As mentioned previously, the historically higher doses of hormonal COCs had a more negative impact on mood. Therefore, initiation of a low dose (10–20 mcg ethinyl estradiol) COC should be considered to minimize side effects, though there is no comparative data to directly support this recommendation. The choice of formulation and route of administration for combined hormonal contraceptives may also be important. Monophasic forms of combined oral contraceptives (COCs) are thought to have greater benefit for menstrually linked mood symptoms than triphasic forms [31], which may be linked to the stability in hormonal levels. For women who were found to have a greater degree of premenstrual symptoms during the hormone-free interval of a traditional 21 active pill/7 day hormone-free pill regimen, continuous administration resulted in greater improvement in premenstrual symptom scores compared with the traditional regimen

[52]. A study comparing low dose oral COCs with the contraceptive vaginal ring found fewer negative mood changes in those utilizing rings [53]. This benefit may be related to the decreased systemic hormone levels seen with vaginal administration or a more continuous, steady release of hormones [31].

Non-hormonal methods should logically have the least impact on mood symptoms, and the lowest dose hormonal contraceptives include IUDs, the ring, and some COCs. In patients with concern for mood side effects, it may be prudent to avoid long-acting higher dose options such as depot medroxyprogesterone acetate injections since the effect cannot be reversed and mood symptoms may persist even past the 12-week dosing interval. Finally, all women should be encouraged to schedule a follow-up visit after initiation of hormonal contraception if they notice any adverse changes in mood.

Conclusions

Although the limited data suggest minimal effects of hormonal contraception on healthy women and women with MDD and bipolar disorder, individual experiences may vary and adolescents as a group may be more vulnerable. Clinicians should evaluate each patient's prior contraception history, any change in affective symptoms in relation to these contraceptive methods, and the presence of hormonally sensitive symptoms (e.g., premenstrual, perinatal, or perimenopausal symptoms and mood changes when taking contraception/hormonal treatment in the past). This approach will allow for the ability to plan for any possible adverse affective symptoms or to prevent them. For women initiating COCs to treat symptoms of PMDD, use of drospirenone-based pills may be effective as a treatment regimen. Prescribers should be aware of potential interactions that might impact contraceptive efficacy, monitor for any correlation between hormonal contraception and affective symptoms that could be explained by medication interactions, and anticipate potential interactions for women on lamotrigine.

Compliance with Ethical Standards

Conflict of Interest Dr. Roe reports grants from Sebela Pharmaceuticals, outside the submitted work.

Dr. Kumar-Kaparaboyna has nothing to disclose.

Dr. Nathan has nothing to disclose.

Dr. Dutton has nothing to disclose.

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.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: lifetime prevalence, chronicity and recurrence. J Affective Disorders. 1993;29:85–96.
2. Lanza di Scalea T, Pearlstein T. Premenstrual dysphoric disorder. Psychiatr Clin N Am. 2017;40:201–16.
3. Joffe H, Petrillo LF. Treatment of premenstrual worsening of depression with adjunctive oral contraceptive pills: a preliminary report. J Clin Psychiatry. 2007;68:1954–62.
4. Rubinow DR, Hoban MC, Grover GN, Galloway DS, Roy-Byrne P, Andersen R, et al. Changes in plasma hormones across the menstrual cycle in patients with menstrually related mood disorder and in control subjects. Am J Obstet Gynecol. 1988;158:5–11.
5. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med. 1998;338:209–16.
6. Andréen L, Nyberg S, Turkmen S, van Wingen G, Fernández G, Bäckström T. Sex steroid induced negative mood may be explained by the paradoxical effect mediated by GABAA modulators. Psychoneuroendocrinology. 2009;34:1121–32.
7. Maguire J, Mody I. $GABA_AR$ plasticity during pregnancy: relevance to postpartum depression. Neuron. 2008;95:207–13.
8. Osbourne LM, Gispen F, Sanyal A, Yenokyan G, Mellman S, Payne JL. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. Psychoneuroendocrinology. 2017;79:116–21.
9. Klaiber EL, Broverman DM, Vogel W, Peterson LG, Snyder MB. Individual differences in changes in mood and platelet monoamine oxidase (MAO) activity during hormonal replacement therapy in menopausal women. Psychoneuroendocrinology. 1996;21:575–92.
10. Payne JL. The role of estrogen in mood disorders in women. Int Rev Psychiatry. 2003;15:280–90.
11. Joffe H, de Wit A, Coborn J, Crawford S, Freeman M, Wiley A, et al. Impact of estradiol variability and progesterone on mood in perimenopausal women with depressive symptoms. J Clin Endocrinol Metab. 2020;105(3).
12. Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression: results from the Massachusetts Women's Health Study. Ann Epidemiol. 1994;4(3):214–20.
13. Joffe H, Cohen LS. Estrogen, serotonin, and mood disturbance: where is the therapeutic bridge? Biol Psychiatry. 1998 Nov 1;44(9):798–811.
14. Toffoletto S, Lanzenberger R, Gingnell M, Sundström-Poromaa I, Comasco E. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: a systematic review. Psychoneuroendocrinology. 2014;50:28–52.
15. Grant EC, Pryse-Davies J. Effect of oral contraceptives on depressive mood changes and on endometrial monoamine oxidase and phosphatases. Br Med J. 1968;3:777–80.
16. Westhoff CL, Heartwell S, Edwards S, Zieman M, Stuart G, Cwiak C, et al. Oral contraceptive discontinuation: do side effects matter? Am J Obstet Gynecol. 2007;196:412.e1–6.
17. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol. 1998;179:577–82.

18. Keyes KM, Cheslack-Postava K, Westhoff C, Heim CM, Haloossim M, Walsh K, et al. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. Am J Epidemiol. 2013;178:1378–88.
19. Skovlund CW, Morch LS, Kessing LV, Lidegaard O. Association of hormonal contraception with depression. JAMA Psychiatry. 2016;73:1154–62.
20. Skovlund CW, Morch LS, Kessing LV, Lange T, Lidegaard O. Association of hormonal contraception with suicide attempts and suicides. Am J Psychiatry. 2018;175:336–42.
21.•• Lundin C, Danielsson KG, Bixo M, Moby L, Bengtsdotter H, Jawad I, et al. Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle: a double-blind, placebo-controlled randomized trial. Psychoneuroendocrinology. 2017;76:135–43 **One of the few randomized controlled trials comparing combined oral contraceptives versus placebo, which showed minimal mood effects and no effect on depression.**
22. Graham CA, Ramos R, Bancroft J, Maglava C, Farley TM. The effects of steroidal contraceptives on the well-being and sexuality of women: a double-blind, placebo-controlled, two-centre study of combined and progestogen-only methods. Contraception. 1995;52:363–9.
23. Berenson AB, Odom SD, Breitkopf CR, Rahman M. Physiologic and psychologic symptoms associated with use of injectable contraception and 20 microg oral contraceptive pills. Am J Obstet Gynecol. 2008;199:351.e1–12.
24. Toffol E, Heikinheimo O, Koponen P, Luoto R, Partonen T. Hormonal contraception and mental health: results of a population-based study. Hum Reprod. 2011;26:3085–93.
25. Steinberg JR, Tschann JM, Henderson JT, Drey EA, Steinauer JE, Harper CC. Psychological distress and post-abortion contraceptive method effectiveness level chosen at an urban clinic. Contraception. 2013;88:717–24.
26. Civic D, Scholes D, Ichikawa L, LaCroix AZ, Yoshida CK, Ott SM, et al. Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. Contraception. 2000;61:385–90.
27. Zettermark S, Vicente RP, Merlo J. Hormonal contraception increases the risk of psychotropic drug use in adolescent girls but not in adults: a pharmacoepidemiological study on 800 000 Swedish women. PLoS One. 2018;13(3):e0194773.
28. de Wit AE, Booij SH, Giltay EJ, Joffe H, Schoevers RA, Oldehinkel AJ. Association of use of oral contraceptives with depressive symptoms among adolescents and young women. JAMA Psychiatry. 2020;77:52–9.
29. O'Connell K, Davis AR, Kerns J. Oral contraceptives: side effects and depression in adolescent girls. Contraception. 2007;75(4):299–304.
30. McKetta S, Keyes KM. Oral contraceptive use and depression among adolescents. Ann Epidemiol. 2019;29:46–51.
31. Kristjansdottir J, Sundelin C, Naessen T. Health-related quality of life in young women starting hormonal contraception: a pilot study. Eur J Contracept Reprod Health Care. 2018;23(3):171–8.
32. Schaffir J, Worly BL, Gur TL. Combined hormonal contraception and its effects on mood: a critical review. Eur J Contracept Reprod Health Care. 2016;21:347–55.
33.• Pagano HP, Zapata LB, Berry-Bibee EN, Nanda K, Curtis KM. Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: a systematic review. Contraception. 2016;94:641–9 **A critical review of the limited studies evaluating the use of contraception in patients with mood disorders.**
34. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. Am J Obstet Gynecol. 2002;187:551–5.
35. Peters W, Freeman MP, Kim S, Cohen LS, Joffe H. Treatment of premenstrual breakthrough of depression with adjunctive oral contraceptive pills compared with placebo. J Clin Psychopharmacol. 2017;37:609–14.
36. Maki PM, Kornstein SG, Joffe H, Bromberger JT, Freeman EW, Athappilly G, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. J Women's Health. 2019;28:117–34.
37. Rasgon N, Bauer M, Glenn T, Elman S, Whybrow PC. Menstrual cycle related mood changes in women with bipolar disorder. Bipolar Disord. 2003;5:48–52.
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Arlington: American Psychiatric Association; 2013. p. 171–2.
39.• Rapkin AJ, Korotkaya Y, Taylor KC. Contraception counseling for women with premenstrual dysphoric disorder (PMDD): current perspectives. Open Access J Contracept. 2019;10:27–39 **An excellent overview of the etiology and treatment options for PMDD, with a detailed review of studies evaluating the impact of hormonal contraception.**
40. Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of perimenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception. 2005;72:414–21.
41. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol. 2005;106:492–501.
42. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database Syst Rev. 2012;2:CD006586.
43. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. Obstet Gynecol. 2000;95(2):261–6.
44. Halbreich U, Freeman EW, Rapkin A, Cohen LS, Grubb GS, Bergeron R, et al. Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. Contraception. 2012;85:19–27.
45. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106:1071–83.
46.•• Ti A, Curtis KM. Postpartum hormonal contraception use and incidence of postpartum depression: a systematic review. Eur J Contracept Reprod Health Care. 2019;24(2):109–16 **This recent review evaluated the available evidence for any interaction between contraceptive method selection and development of postpartum depression, with the conclusion that there is no consistent association.**
47. Roberts TA, Hansen S. Association of hormonal contraception with depression in the postpartum period. Contraception. 2017;96:446–52.
48. Worly BL, Gur TL, Schaffir J. The relationship between progestin hormonal contraception and depression: a systematic review. Contraception. 2018;97:478–9.
49. Lawley ME, Haddad L, Burley K, Farr SL. Use of contraception among US women reporting postpartum depressive symptoms, pregnancy risk assessment monitoring system 2009-2011. Contraception. 2018;97:29–33.
50. Berry Bibee EN, Kim M, Simmons KB, Tepper NK, Riley HEM, Pagano HP, et al. Drug interactions between hormonal

contraceptives and psychotropic drugs: a systematic review. Contraception. 2016;94:650–67.
51. Perry R, Stone RH, Haider S. Medication interactions with contraceptives. In: Allen RH, Cwiak CA, editors. Contraception for the medically challenging patient. New York: Springer Science + Business Media; 2014. p. 347–62.
52. Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. Am J Obstet Gynecol. 2006;95:1311–131.
53. Sabatini R, Cagiano R. Comparison profiles of cycle control, side effects and sexual satisfaction of three hormonal contraceptives. Contraception. 2006;74:220–3.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.