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Progesterone, reproduction, and psychiatric illness

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Abstract

Mood and anxiety disorders are vastly overrepresented in women, and one important contributor to these differences is the fluctuation in sex steroids in women during the reproductive years. Considerable evidence supports a role for abnormal sensitivity to these hormonal fluctuations for some women, who develop mood symptoms associated with reproductive transitions. This chapter presents evidence of the role of endogenous progesterone and its metabolites in such mood symptoms, and then goes on to cover the evidence concerning exogenous progesterone's effects on mood. Overall, the literature does not support an association between exogenous progesterone and negative mood in the general population, but does indicate that subset of women may be vulnerable to such effects. Research is lacking on women with psychiatric illness.

Keywords

Mood; Anxiety; Reproduction; Progesterone; Allopregnanolone; Contraception

Introduction

Mood and anxiety disorders are vastly overrepresented in women, with major depressive disorder (MDD) and most anxiety disorders twice as common in women as in men [1]. These stark sex differences arise from many causes, including differences in brain structure and function as well as behavioral differences arising from cultural expectations and stereotypes. One important contributor to these differences is the fluctuation in sex steroids in women during the reproductive years (and consequent effects on other systems, such as the hypothalamic-pituitary-adrenal (HPA) axis and the immune system) [2]. Mood and anxiety symptoms that occur at times of reproductive transition (including menarche, the menstrual cycle, pregnancy and postpartum, and perimenopause) can offer us a unique window to observe the role of sex steroids. To date, the vast majority of existing literature supports a role for sex steroid fluctuations (rather than differences in absolute levels) in reproductive affective symptoms [3]. Some literature has supported a role for estrogen

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withdrawal in postpartum depression (PPD), but studies have been equivocal on whether treatment with estrogen may help symptoms of PPD [4,5]. Dysregulation of progesterone and its metabolites, on the other hand, appears to play a prominent role, though the nature of that role is still much in dispute. While some evidence supporting this role comes from basic and translational studies of endogenous progesterone, other insights come from literature exploring the effect on mood of progesterone treatments (for contraception, for sustaining pregnancies, or for symptoms of menopause) (see Table 1).

In this chapter, we will first review the role of endogenous progesterone and its metabolites (focusing chiefly on allopregnanolone (ALLO), the 3-α, 5-α reduced metabolite, and a strong allosteric modulator of the GABA-A receptor) in mood and anxiety symptoms at times of reproductive transition. We will then cover the literature on exogenous progesterone treatments and their relationship to mood and anxiety symptoms; the two sections together will offer a broad overview of current information about the relationship between progesterone and mood and anxiety symptoms.

Progesterone and allopregnanolone in premenstrual symptoms

Early work on premenstrual mood dysregulation looked at progesterone itself. Progesterone was known to be increased following stress [6,7], and some literature suggested that progesterone might modify 5-HT1A receptors and act as a sedative following stress [6]. Animal literature specifically on the premenstrual period produced some evidence that high progesterone levels might induce mood and anxiety symptoms [8], but other studies showed that progesterone withdrawal [9] or progesterone antagonists (which mimic progesterone withdrawal and/or decreased progesterone receptor activity) [10,11] could lead to increased depressive-like behaviors. Human literature was also mixed. Some studies showed evidence of lower progesterone or a higher estrogen to progesterone ratio in symptomatic women during the premenstrual period [12–14]. Some found that cyclical increases in progesterone were associated with increased mood symptoms premenstrually, but only in women with a history of physical abuse [15]. Other studies found no relationship at all between progesterone levels and premenstrual mood [16–19]. Some posited that the problem lay in acute changes in ovarian steroids, or in the rapidity of decline of progesterone, rather than enduring differences in levels [20,21]. Over 30 years of work, there was no consistent relationship found between progesterone and mood in the premenstrual period [22]. Yet there remained significant evidence that ovarian suppression could eliminate symptoms [23–25], and that add-back of progesterone and estrogen after suppression could reinstate symptoms [24,26]. Most recently, in a study that examined 20 women with premenstrual syndrome (PMS) and 21 healthy controls, researchers concluded that, when symptoms are redefined as occurring perimenstrually rather than premenstrually, there is an association with both lower steady-state progesterone levels and a decline in the luteal phase [27].

When no consistent relationship was found with progesterone, researchers began also to consider the active metabolites of progesterone, and in particular ALLO. Some evidence pointed to increased levels of ALLO in the luteal phase in symptomatic women, and an improvement in symptoms when ALLO was blocked [28]. Other evidence, however, belied such a simplistic relationship, and pointed to LOWER stress reactivity in those with greater

ALLO increases across the luteal phase [29] or to a failure of women with premenstrual dysphoric disorder (PMDD) to mount the expected stress-related increases in ALLO [30]. This led some to conclude that ALLO operated with an inverted U-shaped curve of reactivity in vulnerable women, with normal luteal phase levels being anxiogenic for women with PMDD, but both high and low levels being anxiolytic [31–33], while others have concluded that it is a vulnerability to change rather than level that is responsible [34,35]. Additional evidence over the last few years has supported the notion that symptomatic women have an altered sensitivity to the change in normal levels across the luteal phase [36–39], and that levels of ALLO in women with PMDD may be associated with altered HPA axis function [40]. We can, therefore, conclude with confidence that differential sensitivity to ALLO (rather than any alteration in progesterone itself) plays a central role in symptoms of PMDD–though the cause of that differential sensitivity remains in question [41].

Progesterone and allopregnanolone in pregnancy and postpartum

As with PMDD, early researchers in depression during pregnancy and postpartum attempted to find differences in levels of the major sex steroids, estrogen, and progesterone. One early study found more negative mood states during late pregnancy, a time of high progesterone, than during the postpartum, but failed to find a relationship with progesterone levels [42]. Some studies concluded that the progesterone withdrawal at childbirth was a causative factor in PPD [3,43,44], or that progesterone withdrawal led to increased anxiety-like behavior [45]; others found HIGHER levels of progesterone in symptomatic women with postpartum blues [46]; and yet other studies found no relationship in either direction [47–50]. Studies have also looked at the magnitude of change in progesterone across parturition, and results have been mixed [51,52]. Taken together, this evidence indicates that we have no conclusive proof that women who develop antenatal or PPD have either different levels of progesterone or larger or more rapid withdrawals following parturition [35].

Evidence for ALLO alterations in antenatal and postpartum mood is also mixed, though perhaps with a stronger indication for some kind of dysregulation (albeit uncertain in which direction and whether involving altered levels, altered sensitivity, or changes in receptor plasticity). Low ALLO has been correlated with higher depression scores in the third trimester [53], with greater negative emotional symptoms in the second trimester [54], and, when measured in the second trimester, with higher mood and anxiety symptoms in the postpartum [55,56]. But ALLO has also been positively associated with perinatal anxiety symptoms [57], and others have found no relationship at all [58]. Some evidence points to alteration in GABA-A receptors as the mediator of the relationship between ALLO and mood in the peripartum. Those studies that have found a relationship between ALLO and subsequent, but not concurrent, symptoms indicate that other systems (receptor plasticity, gene expression, and rate-limiting enzymes) may be involved. This theory is supported by animal literature indicating that an inability to recover receptor concentration after downregulation during pregnancy–or to appropriately re-calibrate among different subunits of the GABA-A receptor–may underlie postpartum symptoms [59–61].

Progesterone and perimenopausal depression

Depressive symptoms, occurring either de novo or as a relapse of a MDD, are common in the perimenopausal periods, with a –two- to fourfold increase in risk as women traverse the menopausal period [62–65]. However, as women enter the postmenopausal period, their risk of depression actually declines with a significantly lower risk two years after their final menstrual period [66]. Individual sensitivity to fluctuating levels of estradiol likely contributes to this risk of perimenopausal depression [67,68]. Experimental withdrawal of exogenous estradiol in postmenopausal women with a history of perimenopausal depression resulted in clinically significant depressive symptoms, while women with no history did not experience depressive symptoms [69]. The role of progesterone in increasing the risk of depressive symptoms at menopause has not been well studied at all. There do not appear to be any studies looking directly at progesterone levels and psychiatric disorders in this time period. Only one study was identified that looked at levels of ALLO, an active metabolite of progesterone, in perimenopausal depression. It was a cross-sectional study of 140 women with climacteric symptoms, which found that ALLO levels were lower in postmenopausal women versus women who were in perimenopause, and that lower levels of ALLO correlated with depressive symptoms only in the postmenopausal women [70].

While there is clearly considerable work yet to be done to tease out the exact nature of ALLO's role in reproductive affective symptoms, it is clear from the literature cited above that there is a role. Additional research is needed to help us understand what part of that role is due to differences in ALLO levels (either absolute or fluctuations), what part is due to receptor plasticity, and what part involves interactions with other systems, such as the HPA axis and the immune system. Moreover, the lack of consistent findings with progesterone itself, and the relatively more robust findings for ALLO, cannot lead us to conclude that ALLO alone among the neuroactive steroids is at fault. We do not yet know what role other progesterone metabolites may be playing in mood and anxiety symptoms, and the rich line of research on ALLO should not dissuade researchers from asking similar questions about the other progesterone metabolites.

Exogenous progesterone

Exogenous and synthetic forms of progesterone (called "progestins") are used across a woman's life span to address a variety of gynecologic concerns, including menstrual irregularity, heavy or painful periods, perimenopausal transitions and, most commonly, for contraception. Hormonal contraception, in particular, is widely used by reproductive-aged women, and its use has increased substantially with the creation of diverse delivery options. National surveys estimate that 67% of women rely on hormonal methods [71] and 80% of women report having used hormonal contraception at some point in their life [72]. However, since the introduction of combined oral contraception (COC) in the 1960s, psychological side effects (specifically depressive symptoms, mood swings, and irritability) have been reported by contraception users [73,74] and cited as primary cause of discontinuation[75]. Early scientific reports found rates of depressive symptoms ranging from 16 to 56% among women on COC [76]. Since that time, and with the advent of both lower dose pills and alternative delivery methods, concerns about mood side effects have faded. Even today,

however, the majority of hormonal contraceptives have “depression” and “mood changes” listed as a possible side effect, and mood-related side effects continue to contribute to discontinuation and non-compliance [77,78]. Although scientific research exploring the biological connections between sex hormones and mood symptoms has expanded, the underlying etiology of hormonally induced mood symptoms among contraception users remains inconclusive. Without a clear understanding of the biological mechanisms (e.g. how or which hormonal constituents in contraception contribute the observed effects), providers remain limited in their ability to provide adequate counseling or identify populations of women who may be at elevated risk for mood effects.

Therefore, this portion of the chapter will provide an overview of the role of exogenously administered progesterone and progestins, and review the literature on the relationship between these and mood symptoms. The first section will focus on different types of progestin-based contraceptives by delivery modality, then explore two notable studies in depth, and lastly, review the literature on mood effects in particular psychiatric and gynecologic populations.

Mood effects by contraception delivery type

Injectable: Depot medroxyprogesterone acetate (DMPA) was the first non-oral formulation of hormonal contraception available in the United States, and early studies showing an association between DMPA and mood symptoms led to the Food and Drug Administration (FDA) warnings about contraception and mood. The results from two early prospective descriptive studies published in 1996 and 1997 reported high discontinuation rates at 1 year (47% and 71%, respectively), with 6% (N = 18) of those stopping DMPA citing depression as the reason for discontinuation and up to 9% reporting ongoing depressive symptoms at 3 months following DMPA initiation [79,80]. Next, two studies by Westhoff and colleagues (1998) assessed for symptoms of depression with DMPA, but did not find a significant association [81,82]. Most recently, two large prospective studies, both using validated scales for depressive symptoms and control groups, provided conflicting results. First, Civic et al. (2000) compared depressive symptoms and discontinuation rates among 183 DMPA users compared with 274 non-users over the course of 3 years. Compared with non-users, the DMPA cohort had higher symptoms of depression overall (OR: 1.44; 95% CI: 1.00–2.07), prior to (OR: 2.30; 95% CI 5 1.42–3.70), and just following discontinuation (OR: 2.46; 95% CI: 1.46–4.14). Interestingly, depressive symptoms reduced following discontinuation and were not statistically significantly different from those of non-users by 1 year [83]. Although the authors of this study controlled for history of depression, the DMPA group had higher symptoms of depression at study initiation, limiting any conclusions on causality. In the most recent study, Berenson et al. (2008) compared rates of depressive and anxiety symptoms (using the Beck Depression Inventory (BDI) and the Positive and Negative Syndrome Scale (PANSS)) prior to contraception initiation and then every 6 months over the course of 2 years among participants who elected to start one of the three contraceptive forms: DMPA (N = 219), COC (N = 218), and non-hormonal contraception (N = 171) [84]. There were no differences in psychiatric symptomatology among groups. However, this study is limited by a high attrition rate, with more than 50% of participants lost to follow up

in each study arm by 2 years. To date, there are no randomized controlled trials (RCTs) assessing the risk of depressive symptoms.

Subdermal Implant: The subdermal contraceptive implant was developed in the 1980s. The original implant was composed of six rods containing the more androgenic progestin, levonorgestrel (LNG) [85]. The more recent versions, containing two rods, initially release 60–70mcg/day of etonogestrel (ENG; a 3-keto derivative of desogestrel) and decrease to 25–30mcg by the end of the third year. Early descriptive studies among women using the LNG formulation of the subdermal implant found a subset of women with "depressive symptoms" or "mood changes." In a small retrospective analysis, Berenson et al. (1988) found that 33% (N = 21) of adolescents and 17% (N=30) of adults reported mood changes at 6-month post-LNG initiation [86]. Other studies assessing the tolerability of the LNG devices found that 1.3–9% of participants discontinued LNG due to mood-associated changes [87–89]. However, these studies were limited by lack of pre-LNG assessment, standardized measures, and covariate adjustments. Westhoff et al. (1998) prospectively assessed depressive symptoms using the Mental Health Inventory (MHI) among a total of 910 women prior to and up to 2 years following LNG implant initiation [88]. Although their findings did not support an associated worsening of depressive symptoms among women who continued on the LNG implant, there was a large subset of women who discontinued the implant, of which 4.4% cited depressive symptoms as reason for termination. To date, there has only been one study assessing mood symptoms among women using the more recent ENG subdermal implantable rod, which was limited by small sample size (N = 10) and lack of standardized measures. More recent studies assessing the tolerability of ENG (compared with LNG) have not assessed mood symptoms at all [85], and there are no RCTs on either LNG or ENG formulations to date. Going forward, it will be particularly important for prospective studies evaluating mood changes among women on the more recent ENG containing subdermal implants to measure psychological symptoms at multiple time points over the course of 3 years in order to capture potential mood changes associated with the decreasing ENG levels.

Long-Acting Intrauterine Devices (IUDs): Long-acting intrauterine devices (IUDs) are currently the most widely prescribed form of birth control in the US and Europe [90]. Because the IUD provides its contraceptive action through local release of progestin (LNG) on uterine tissue, systemic effects, and by extension mental health side effects, were hypothesized to be lowered. However, systemic circulation remains detectable [91], and one study noted increased stress-reactivity among LNG–IUD users [92]. Studies among women treated with LNG–IUDs for menorrhagia (one of which is an RCT that took release rates of LNG into account) did not support any negative mood sequalae, and the latter showed an increase in BDI scores following LNG–IUD removal (though this may have been related to a return of menorrhagia) [93,94]. Similarly, a Finnish-based cohort study compared a total of 212 LNG–IUD users with non-users and did not find an increase in scores on the BDI or psychiatric diagnoses. There are no studies to date prospectively assessing differences in mood symptoms between the different dose formulations of LNG–IUDs, and the majority of studies are limited in generalizability as they have largely assessed mood symptoms among women using LNG–IUDs for specific gynecologic complaints.

Oral contraception

Formulation: In assessing the role of progestin on mood changes, it has remained unclear if it is the absolute doses of progestin in oral contraception or the changes in progestin doses that underlie mood effects. In theory, if it is the absolute levels of progestin conferring the mood effects, triphasic formulations, which have lower overall progestin levels, would be expected to have reduced mood impact. In two studies, however, the opposite was observed, with greater negative mood symptoms among the triphasic COCs users [95,96] than among women on monophasic formulations. In an elegantly designed prospective study by Coffee et al. (2006), women were first assigned to a triphasic followed by a monophasic formulation of COCs [97,98].

The authors found that the women who had the most severe mood variability while using the COC cyclically experienced the greatest improvement when placed on the monophasic regimen [99]. Together these data suggest that, certainly among some vulnerable women, it may be the changing levels of hormones rather than absolute levels that confer the negative psychological effects. Certainly, this is supported by the biological data (discussed in the endogenous section of this chapter and below) among women with PMDD and perinatal mood/anxiety disorders.

Type of Progestins in Combined Oral Contraception: Aside from dosage and dosing schedule, there is evidence that the chemical properties of the progestin subtypes may play a role in mood symptoms [100]. As outlined above, the earlier generations of progestins contained in oral contraceptive pills (OCPs) had androgenic properties and resulting physical side effects. Aside from the physical side effects, a number of studies also evaluated for differences in mood symptoms among progestin subtypes. An RCT comparing a second-generation LNG-containing OCP with a third-generation desogestrel-containing OCP showed a statistically significant increase in positive symptoms (as measured by the Positive and Negative Affect Scale (PANAS)) and reduction in negative symptoms among women randomized to the third-generation OCP, and the converse for the second-generation OCP [101]. Another study observed improvement in symptoms of “tiredness, depression, moodiness, anxiety, and anger” among women switching from alternative OCPs to an OCP containing the third-generation progestin, gestodene [102]. Additional studies, which support these findings, are summarized in the excellent review by Schaffir et al. (2016) [103].

Most recently, a new progestin called drospirenone–a derivative of 17 α-spironolactone with antiandrogenic activity–has been compared to prior progestins on mood outcomes with promising results. Two RCTs have demonstrated improvement of premenstrual-related mood symptoms among women on a COC containing drospirenone as compared to LNG, including statistically significant reductions in symptoms of “anxiety,” “irritability,” and feeling “sad/blue” using the Women’s Health Assessment Questionnaire (WHAQ) [104,105]. Lastly, the newest formulation of COC, containing a non-androgenic progestin, nomegestrol acetate (NOMAC), and a new estradiol (17-beta-estradiol), has also shown positive mood effects, but additional studies are needed to separate the relative effects of the progestin and estradiol components of this COC [106].

Progestin-Only Oral Contraception: Because there is evidence that the presence of estrogen in OCPs alters the effect of progestins on its targets [100,107], some studies have assessed for differences in mood outcomes between users of COCs versus those of progestin-only pills (POPs). Despite this, there are limited studies assessing the effects of POPs on mood. In the one RCT to date (1995), there were no differences in mood symptoms (based on BDI assessments) among a total of 250 women randomly assigned to start an LNG-based POP, a COC, or placebo [108].

Notable large population-based studies on contraception and mood: In one of the most comprehensive evaluations of the association between hormonal contraception and depressive symptoms to date, Skovuland and colleagues (2017) completed a prospective cohort analysis over a mean of 6.4 years among over 1 million women aged 15–34 in Denmark utilizing two national registries [109]. After excluding for an existing diagnosis of depression (as well as other psychiatric diagnoses), they evaluated differences between users of hormonal contraceptives and non-users in first-time use of antidepressants and in subsequent depression diagnoses. Compared with non-users, they found a small increased relative risk (RR) for first-time antidepressant use among users of the patch (norelgestromin; RR: 2.0, 95% CI: 1.76–2.18), followed by the vaginal ring containing ENG (RR: 1.6, 95% CI: 1.55–1.69), the LNG intrauterine system (RR: 1.4, 95% CI: 1.31–1.42), POPs (RR: 1.34, 95% CI: 1.27–1.40), and COCs (RR: 1.23, 95% CI: 1.22–1.25). A similar difference was observed for first-time depression diagnoses. Interestingly, the same pattern of risk emerged after age stratification, but the RR of developing depression or of first-time antidepressant use was higher among adolescents and decreased with age. The increased risk for depression observed among adolescents supports previous data showing a steep rise in MDD during periods of natural hormonal fluctuations [110] (namely, puberty, peripartum, and perimenopause) and may suggest an interaction between the use of exogenous hormones and natural vulnerability.

In a similar study, the aforementioned authors next evaluated the risk of suicide attempts among hormonal contraception users compared with non-users. Compared with non-users, current or recent users of hormonal contraception had a statistically significant risk of first suicide attempt (RR: 1.97, 95% CI: 1.85–2.10, $p < 0.0001$). Risk for first suicide attempt was highest among adolescents aged 15–19 (RR: 2.06, 95% CI: 1.92–2.21), peaked in the first 2 months following initiation among all users, and remained elevated between RR = 2.0 and 2.5 for the first year. Among the subtypes of contraception, the patch carried the highest relative risk (RR: 3.28, 95% CI: 2.08–5.16), followed by the vaginal ring (RR: 2.58, 95% CI: 2.06–3.22), oral progestin products (RR: 2.29, 95% CI: 1.77–2.95), and then COCs (RR: 1.91, 95% CI: 1.79–2.03) independent of ethinylestradiol (EE) dosing.

Both of these studies have substantial strengths; namely, the use of large prospective registry data to control confounding variables and increase the statistical power to detect differences that may have previously gone unrecognized. However, what registry data gain in breadth, it can sometimes lose in depth, making its application to clinical practice, and future research difficult to determine. For example, it is not known whether the association between contraception and antidepressants may be a result of confounding by indication in which the adolescents who elect to start on contraception have different risk factors, including

increased risk for psychiatric illness. Certainly, these data reinforce the need for counseling on mood symptoms, particularly among adolescents and in the first year of contraception use. From a research perspective, registry data can overlook certain vulnerable populations who may be at increased risk for hormonally triggered mood effects. Lastly, while the RR observed in population-based data can help suggest trends, it should be noted that the absolute risk (especially for a rare event like suicide) remains low.

Conclusion

Overall, associations between the forms of progestins in contraception and types of contraception delivery methods with subsequent mood symptoms remain largely inconclusive. While the majority of individual studies have not shown a significant association between progestin-based contraception and onset of mood symptoms for most individuals, there are a subset of women in many of these studies reporting mood changes. It is noteworthy that, in the largest studies to date, in which power is greatly increased, Skovuland et al. (2017) did find an association between contraception and subsequent initiation of psychotropics and suicide. However, both the individual studies and the large-pooled analyses remain limited by the few RCTs completed. Going forward, RCTs specifically evaluating the role of different progestin types (especially newer formulations), dosages, dosage changes, and delivery method that use standardized mood assessments are needed to truly evaluate the link between progestin-based contraception and mood. Additionally, it is critical that future studies also evaluate the association between contraception and symptoms of anxiety and irritability, as this has been largely overlooked in the research to date and is the primary symptom reported among women with PMDD. Lastly, the vast majority of studies have not evaluated the effect of contraception on women with known psychiatric illness, who may be particularly vulnerable to hormonal fluctuations, and therefore, need tailored counseling by their gynecologic practitioners when starting contraception.

Mood effects of progestins on particular psychiatric populations

Because the majority of studies assessing the mood effects of contraception have either excluded women with a history of psychiatric illness or have not controlled for psychiatric history, we will next review the literature to date that specifically evaluates potentially vulnerable psychiatric populations.

Depression: As mentioned previously, many of the studies to date have focused on the onset of depressive symptoms *after* hormonal contraception initiation and have therefore purposefully excluded or controlled for past psychiatric diagnoses. The literature specifically evaluating the effects of hormonal contraception among women with major depression, on the other hand, is very limited. Using the data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, Young et al. (2007) prospectively evaluated a large cohort of women with a primary diagnosis of MDD without psychosis taking different forms of contraception: a total of 234 women taking COCs, 48 on progestin-only methods, and 948 on non-hormonal contraception. Overall, there were no differences in rates of major depressive episodes, though the lack of findings may have been affected by uneven

comparison groups. To this author's knowledge, there are no other prospective studies or RCTs evaluating the association of hormonal contraception and worsening or relapse of depressive episodes among adult women. Given that approximately 60% [111] of women with psychiatric illness are estimated to experience a pre-menstrual exacerbation of psychiatric symptoms, it is particularly important to assess differences in disease trajectory across the menstrual cycle among women with affective disorders on different types of progestin-based contraception.

Bipolar Disorder: Women with bipolar disorder can also suffer from premenstrual exacerbation of mood symptoms. However, given that mood fluctuations are the hallmark of the underlying illness, these premenstrual changes can be difficult to distinguish. Therefore, thorough evaluation for changes in mood symptoms with hormonal contraception can be challenging and is of particular importance. Unfortunately, a systematic review by Pagano et al. (2016) identified only two papers focusing on mood changes among women with Bipolar disorder on various formulations of contraception [112]. In a small prospective study, women on oral contraceptives (OCs; type not specified) had fewer mood fluctuations across their menstrual cycles compared with the women not on OCs [113]. In a large cohort study among women with bipolar on either the DMPA, Cu–IUD, LNG–IUD, or sterilization, no significant differences were noted in relapse of illness nor hospitalization rates [114]. No RCTs evaluating the effects of hormonal contraception on disease trajectory exist.

Anxiety: Despite the high comorbidity of anxiety and depression and the fact that "anxiety" is a frequently listed side effect of hormonal contraception, few studies [14,29–32] have explicitly assessed the presence or changes in anxiety symptoms with hormonal contraception use among women with anxiety disorders. In the above study by Young et al. (2007) among women with MDD, OCD comorbidity was higher among women in the progestin-only group, whereas there were no significant differences in other psychiatric comorbidities across other contraceptive formulations. Unfortunately, there have been no other prospective studies nor RCTs in this population.

Schizophrenia and Schizoaffective: There is one review to date evaluating contraception use among women with Schizophrenia [115]. However, none of the studies reviewed assess the effect of contraception on psychiatric symptoms in this population.

Mood effects of ProgesteronE and progestins on psychiatric symptoms across the reproductive lifespan

Premenstrual Dysphoric Disorder: As detailed earlier in this chapter, women suffering with PMDD experience symptoms of depression, anxiety and/or irritability during the late luteal phase and week preceding the onset of menses. Earlier research measuring total progesterone levels across the cycle did not find any significant differences between women with PMDD and controls, nor great utility in adding back progesterone as a treatment for the symptoms of PMDD [116–119]. Instead recent research supports that the observed mood symptoms are likely a result of an altered sensitivity to changing levels of hormones (the progesterone metabolite, ALLO in particular) at hormone levels drop. Despite the known intersection of hormonal vulnerability and mood symptoms in this population, there is a

paucity of research investigating the effects of non-oral, hormonal contraception [39,120]. The majority of the literature has evaluated the efficacy of different triphasic versus monophasic formulations of oral contraception. In an overview of four studies that evaluated OCs containing a continuous formulation of combination LNG and EE among women with PMDD, variable improvement on the DRSP and a large placebo effect was noted [121]. A RCT among a total of 55 women with PMDD showed a notable placebo effect with overall improvement on premenstrual symptoms across all three arms: intermittent versus continuous formulations of drospirenone/estradiol and placebo [122]. However, since this time, two RCTs evaluating the efficacy of the drospirenone/estradiol formulation on symptoms among women with PMDD have supported its utility; with both studies demonstrating significant and marked (up to 50%) improvement on mood symptoms measured by the Daily Record of Severity of Problems (DRSP) compared with placebo [123,124]. These studies served as the basis for this particular COC formulation (marketed as YAZ) to be the first FDA approved hormonal contraception for the treatment of a menstrual-based psychiatric disorder.

Pregnancy: Exogenous progesterone is used in pregnancy for the prevention of preterm birth (PTB) in those with a history or those with a short cervix [125]. It is also used in luteal phase support in assisted reproductive technology (ART) procedures to increase endometrial receptivity to implantation. It is initiated in the luteal phase of stimulated cycles and is continued until a positive pregnancy test or until the end of the first trimester [126].

There are various formulations of exogenous progesterone. Micronized progesterone, which is a natural form of progesterone, is given vaginally in the form of a gel or a suppository and is usually administered daily. Micronized progesterone can also be given orally; however, bioavailability is poor due to first-pass hepatic metabolism, and sedation also limits its use [127]. Synthetic progesterone, or 17α-hydroxyprogesterone (17-HP), is given as an intramuscular (IM) injection, usually on a weekly basis. It achieves reliable plasma levels but is associated with a number of adverse reactions, such as injection site pain or injury, allergic reaction to the vehicle, and nausea and vomiting. Natural progesterone is associated with fewer side effects and increased patient acceptability and compliance [127,128]. The only drawback is that plasma levels reached are less reliable than with the IM administration. However, this is counter-balanced by the fact that vaginal administration results in local cervical and endometrial effects.

From an extensive review of the literature, there is only one study that directly assesses the psychiatric adverse effects of exogenous progesterone use in pregnancy. It was a prospective, randomized, open-label study of 100 pregnant Iranian women with a history of PTB, who were randomly assigned to vaginal progesterone or 17-OPH in the second trimester. There was an increase in emotional distress scores at 8 weeks post intervention compared with baseline in both groups. However, the groups were not compared with one another in terms of this outcome, nor were there any placebo groups [129].

There have been many studies assessing psychiatric symptoms in women undergoing in vitro fertilization (IVF), with variable and overall inconclusive findings [130–140] However, there have not been any studies specifically looking at progesterone use in IVF and its effect on

mental health. Full texts of RCTs, systematic reviews, and meta-analyses of the use of exogenous progesterone in pregnancy were screened for use of psychiatric measures as secondary outcomes, but none were found. Given the documented adverse psychiatric effects of progesterone in contraception and menopause hormonal treatment, it should be more extensively studied in pregnancy also.

Postpartum Depression (PPD): Many postpartum women opt for progestin-only-based contraception to allow for continued breastfeeding. Because this population is experiencing natural hormonal fluctuations and is at increased risk for depressive episodes [141,142], studies evaluating mood effects of contraception are especially important. Despite this, few studies have evaluated the effects of progestin-based contraceptives on mood symptoms. In an early double-blind RCT, N = 180 women were randomly assigned to receive either a norethisterone or placebo (saline) injection at 48-h postpartum [143]. Overall, prospective evaluation of mood by the Edinburgh Postnatal Depression Scale (EPDS) and the Montgomery–Åsberg Depression Rating Scale (MADRS) showed significantly increased symptoms of depression in the first 3 months. Notably, the depressive symptomatology correlated with the pharmacokinetic activity of the norethisterone; with resolution of depressive symptoms by 3 months post-injection and drug levels falling to 0 by 2 months. Two recent studies evaluating depressive symptoms among postpartum women, this time with DMPA injections, showed conflicting results, with one study showing a worsening of depressive symptoms among DMPA users compared with those using IUDs [144] and another showing reduced rates of postpartum depression among the DMPA users compared with women not using contraception [145]. Lastly, one study demonstrated increased depressive symptoms among women on the ENG implant, but reduced symptoms of depression among women using norethindrone-only pills (POPs) and LNG–IUDs compared with non-hormonal contraception users [146]. Certainly, additional studies are needed before clinicians abstain from using injectable or implantable-based contraceptive modalities among postpartum patients, but these studies reinforce the importance of considering the role progestin-based contraception may have in postpartum mood symptomatology.

Use of exogenous progesterone to treat PPD: The use of progesterone to treat PPD has been investigated to a limited extent in the literature [147]. Four studies were identified, with three of the four being of poor quality. Two of the first studies in the 1980s concluded that progesterone was effective in preventing PPD in those with a prior history. However, both studies were considered unreliable as there was either no control group or the control group consisted of women who refused the intervention [148]. A subsequent study used rectal progesterone in nine women with established PPD in a double-blind cross over placebo-controlled study, with no difference found in depressive symptoms with either the intervention or placebo [149]. Again, the results of this study may not be valid due to the small sample size. A third study compared norethisterone enanthate (depot contraceptive) with placebo in 180 healthy participants within 48 h of delivery and found that there were significantly more depressive symptoms seen in the treatment group [150]. Based on the results of these studies, there is no evidence to support the use of progesterone in the prevention or treatment of PPD.

The use of the progesterone metabolite, ALLO, has also been studied as a treatment for PPD. A synthetic version of ALLO, brexanolone, was investigated recently in a trio of placebo-controlled clinical trials showing that it is superior to placebo in reducing depressive symptom scale scores in women with PPD. The effects seen were abrupt and robust, with 96% maintaining remission from depression at 30 days post infusion [151,152] Based on these findings, brexanaolone has recently been approved by the US FDA for the treatment of PPD [153], making it the only FDA-approved treatment for this illness.

Progesterone and menopausal hormone treatment

Progestins are given as part of menopausal hormone treatment (MHT) solely to prevent endometrial hyperplasia from unopposed estrogen replacement in women with an intact uterus. At the advent of MHT, estrogen was given alone until it was found that unopposed estrogen led to endometrial changes and potentially cancer [154,155]. Historically, medroxyprogesterone acetate (MPA) was used, but this is no longer recommended based on results of the Women's Health Initiative study, which found that it was associated with increased risk of breast cancer, cardiovascular disease, and elevated lipids [156]. Micronized progesterone is now preferred as it is effective in preventing endometrial hyperplasia, but is not associated with the aforementioned adverse effects [157]. It is important to note that although the initial Women's Health Initiative study showed an increase risk of breast cancer and cardiovascular disease with combined MHT, the subsequent study did not find these risks in women transitioning to menopause or in early postmenopause when given in low doses for brief periods [158].

Progesterone in MHT and depression

The balance of evidence available suggests that progesterone in MHT may lead to negative mood symptoms. When investigators look at the effects of estrogen alone on mood [69,159,160] or combined treatment with estrogens and progesterone [68,161–164] on mood, the majority find a beneficial effect. However, when studies separate out the effect of the estrogen from the progesterone, a negative effect on mood is observed once the progestin is added to the treatment regimen [165–167]. One study found that adverse psychological symptoms correlated with timing of administration of progesterone as part of a hormone replacement cycle. Interestingly, this only occurred with a lower dose of progesterone (30 mg daily) versus higher doses (60 mg or 200 mg daily). This study also tested serum hormone levels, finding that intermediate plasma levels of ALLO, rather than high or low, correlated with negative mood symptoms [168]. Two other studies found such an association with lower doses of progesterone, either vaginal progesterone or MPA, being associated with more negative mood symptoms, when compared with higher doses [165,169]. It is not known exactly why lower doses of progesterone in MHT are associated with depressive symptoms, while higher doses are not. Animal models have also shown this phenomenon, with lower doses of progesterone causing aversive and aggressive behavior in mice, whereas higher doses did not (Beauchamp et al.; Fish et al.). It is possible that lower doses of progesterone, through the actions of ALLO, lead to up-regulation of the GABA-A receptor such that it is not fully occupied, leading to an anxiogenic response. Increasing the dose leads to saturation of the receptor by the active metabolites of progesterone, ALLO, and pregnanolone, mediating an anxiolytic response [170].

There are fewer studies that have failed to show an association with progesterone and psychiatric symptoms. One randomized placebo-controlled trial of 54 postmenopausal women receiving either estrogen alone or estrogen/progesterone combination showed a statistically, but not clinically, significant increase in daily depression symptoms at the end of 6 months of MHT in the combination group versus the estrogen-only group [171]. Another study failed to show a negative effect on mood with addition of MPA following estradiol treatment in peri- and postmenopausal women in depressed and non-depressed women [172]. A third study found no association between different doses of progesterone vaginal cream alone (not taking estradiol in combination) and negative mood symptoms in 223 postmenopausal women [173].

Forms of progesterone and Depression: In term of mood effects, there have been only a few studies directly comparing two different progestins effect on mood with varied results. Caglayan et al. (2014) found that MPA was less favorable than dienogest [174], while another group found worse outcomes for norethindrone than MPA, when both were added to estradiol as part of MHT [169]. Dienogest and norethindrone are both forms of progesterone less commonly used in MHT.

Even though there is some evidence showing a benefit from MHT on mood, overall the findings are inconclusive, especially if you consider the studies that have shown a negative effect when mood is assessed before and after addition of progesterone. In addition, menopausal depression is likely a heterogeneous illness with pathophysiology not just related to hormone changes but to other factors, such as the psychosocial and physical changes that accompany menopause. For this reason, antidepressants are still used first-line to treat depressive symptoms in menopause, with preference given to particular ones (paroxetine and venlafaxine), if hot flashes are comorbid [175]. Women given a combination MHT consisting of estrogen and a progestin, for indications other than mood, should be monitored for emergence of depressive symptoms during treatment. Future research should investigate why lower doses of progesterone lead to negative mood symptoms, whereas higher doses do not. Studies could measure the activity of the GABA-A receptor to see whether it is over-expressed at lower doses of progesterone administration. In addition, defining threshold doses of progesterone in MHT, above which there is not an association with negative mood, would be useful in designing MHT formulations.

Conclusion

The biological basis underlying the natural hormonal fluctuations occurring across a woman’s lifespan, the use of exogenous progesterone and progestin derivatives, and the complex interaction these may (or may not) have on subsequent mood symptoms remains an area rich for scientific exploration. To date, research indicates that some vulnerable women experience mood symptoms associated with normal physiological hormonal fluctuations at times of reproductive transition, and it seems likely that vulnerability lies in sensitivity to the progesterone system. Overall, the literature thus far does not support an interaction of synthetic progestins or progesterone and negative mood symptoms for the majority of women. However, the research does indicate that there is a subset of women who may either benefit from or worsen from certain types of progestins (sensitivity to androgenic

component of earlier progestins), progestin formulations (monophasic or triphasic), delivery method, or timing in their cycle or across their lifespan. It is, therefore, critical that practitioners have an appreciation for the potential psychiatric side effects (both positive and negative) when starting any progesterone or progestin-based product and that women are monitored for changes in symptoms of depression, anxiety, and mood cycling. Without proper counseling about the potential mood side effects, non-compliance may continue or women may remain on progestin-products while unknowingly suffering from psychological side effects that can lead to increased morbidity or even mortality.

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Practice points

- Altered sensitivity to fluctuations in gonadal steroids is associated with mood symptoms in vulnerable women.
- Considerable evidence points specifically to a role for allopregnanolone (ALLO), and this may partially explain the etiology of premenstrual dysphoric disorder (PMDD) and postpartum depression (PPD).
- Women with PMDD may benefit from treatment with hormonal contraception.
- Women with PPD may benefit from treatment with synthetic ALLO, recently approved by the Food and Drug Administration and the first drug ever approved for PPD.
- There is no evidence that treatment with progesterone derivatives is helpful for any other types of mood symptoms, so no basis for prescribing them for this purpose.
- There is limited evidence about the adverse mood effects of progesterone-only contraception, and limited evidence about effects of hormonal contraception on women with known psychiatric illness. Women's individual experience should guide prescribing in these cases until further evidence is available.
- There is limited evidence about the mood effects of progesterone derivatives used in infertility treatment or to sustain pregnancy.
- Some recent large population-based studies found an increase in mood symptoms after initiation of both combined and progesterone-only hormonal contraception (compared with non-users), but these data do not account for many differences between the two groups.
- There is some evidence of increased adverse mood symptoms in women taking combined menopausal hormone treatment compared with women using estrogen-only menopausal hormone treatment.

Research agenda

Additional research is crucially needed in the following areas:

- Etiology of individual sensitivity to normal hormonal fluctuations.
- Effects of progesterone supplementation in pregnancy on mood.
- Effects of progesterone-only contraceptives on mood in women with psychiatric illness.
- Usefulness (or lack thereof) of synthetic allopregnanolone for other reproductive-associated mood symptoms, or for prevention.

Table 1

Treatments for mood and anxiety disorders in women.

Reproductive Stage/ Psychiatric Illness	Recommended Treatment			Notes
Depression	Selective Serotonin Re-uptake Inhibitors (SSRIS) are first line. E.g.			No evidence that treatment with progesterone derivatives is helpful Psychologytoday.com to find therapists practicing CBT in your area.
	Name	Starting Dose (mg)	Target Dose (mg)	
	Sertraline	25	50–150	
	Citalopram	10	20–40	
	Escitalopram	5	10–20	
	Fluoxetine	10	20–60	
Anxiety	Same as Depression			As above
Premenstrual Dysphoric disorder	• SSRIs (as above): given during symptom-onset, luteal, or continuous. • *Drospirenone* 3mg*/ethinylestradiol 0*.2 mg *daily* (e.g. "Yaz") dosed 24–2 or continuously • Gonadotropin-releasing hormone (GnRH) analogs (leuprolide 37.5 mg monthly) • GnRH analogs and stable hormone add-back (estradiol or progesterone) • Cognitive behavioral therapy (CBT) and dialectical behavioral therapy (DBT)			Iapmd.org for PMDD resources and treatment guidelines. Psychologytoday.com to find therapists practicing CBT and DBT in your area.
POSTPARTUM DEPRESSION	• SSRIs (as above) • May benefit from treatment with synthetic allopregnanolone (brexanolone), the first drug ever approved for PPD • CBT and interpersonal therapy (IPT)			https://www.postpartum.net/
Perimenopausal Depression/ anxiety	• SSRIS (as above) for mood symptoms. • For vasomotor Symptoms: – Venlafaxine: 37.5–75 mg – Paroxetine: 10 mg – Citalopram: 10–20 mg – Fluoxetine: 10–20 mg – Gabapentin: 300–900 mg – Clonidine: 0.1 mg transdermal patch			Some evidence of increased adverse mood symptoms in women taking combined menopausal hormone treatment compared with women using estrogen-only MHT. OCPs can be also be used to treat mood when women also have physical symptoms of menopause, but are not first line for mood alone.