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Review article

Oral contraceptives and mood in women with and without premenstrual dysphoria: a theoretical model

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Summary

Despite numerous studies on the topic, there is no consensus to date on the effects of oral contraceptives on mood or the mechanism(s) by which they exert these effects. This review article presents a theoretical model to explain the way in which oral contraceptives may affect mood. Specifically, it is argued that progestins exert differential effects on endogenous levels of neurosteroids, thereby altering mood. After providing an overview of the effects of estrogen, progesterone, and progesterone's metabolites on cortical excitability and the role of neurosteroids in depression and premenstrual dysphoria, this article reviews the research that has been conducted on the relationship between oral contraceptives and neurosteroids. Finally, suggestions for future research are made with the dual aim of improving existing studies on the relationship between oral contraceptives and mood and further investigating the possibility that fluctuations in neurosteroid levels are responsible for the effects of oral contraceptives on mood.

Keywords: Oral contraceptives; neurosteroids; GABA; allopregnanolone; mood.

Introduction

With over 100 million women worldwide using oral contraceptives (OCs) (Petitti, 2003) and depression being cited as the primary reason for OC discontinuation (Sanders et al., 2001), there is a clear rationale for investigating the effects of OCs on mood. However, there is a relative dearth of knowledge regarding the central nervous system (CNS) effects of OCs. Multiple lines of investigation indicate that 17-beta estradiol, the most potent estrogen produced by the ovaries, progesterone, and the progesterone derivative allopregnanolone have significant modulatory effects upon neurotransmitter systems involved in the regulation of affect and behavior (Bethea et al., 1998; Epperson et al., 1999; McEwen et al., 1999). Yet, the degree to which the CNS effects of the estrogens and progestins incorporated in most OCs are similar to those of their naturally occurring counterparts is not known. In addition, standard and extended-cycle OC regimens do not mimic the normal menstrual cycle as they expose women to an estrogen and a progestin on a daily basis for 3 weeks and 3 months, respectively. While previous reviews have proffered several mechanisms by which OCs could modulate mood/affect, this article will focus primarily on evidence suggesting that baseline abnormalities in the gamma-aminobutryic acid (GABA) neuronal function predispose women with PMDD to OC-induced mood worsening and that OCs in general exert their effect on mood by altering the balance between cortical excitation and inhibition.

How might OCs modulate mood?

Several mechanisms by which OCs may affect mood in vulnerable women have been proposed. Estrogen is known to reduce pyridoxine, which is a co-factor in a number of enzymatic reactions. A deficiency in this co-factor could, theoretically, contribute to reductions

in neurotransmitters, such as serotonin (5-HT) and norepinephrine, known to play a role in the regulation of affect and behavior (Leeton, 1974; Winston, 1973). However clinical and preclinical studies indicate that estrogen has multiple 5-HT enhancing effects. Estrogen administration increases mRNA for tryptophan hydroxylase, the rate-limiting enzyme for 5-HT production (Pecins-Thompson et al., 1996). Estrogen also enhances 5-HT_{2a} receptor mRNA in the dorsal raphe nucleus (Sumner & Fink, 1993) and 5-HT_{2a} receptor binding in the cerebral cortex and nucleus accumbens in ovariectomized female rats (Sumner & Fink, 1995). In humans, positron emission tomography studies indicate that estrogen administration increases the density of 5-HT2_{A} receptors in menopausal women (Kugaya et al., 2003).

Although estrogen has extensive effects on 5-HT function, it is difficult to attribute the depressogenic effects of OCs in some individuals to the estrogen-5-HT interaction, as this interaction would seem to be mood enhancing. Additionally, neither estrogen's effects on pyridoxine nor on 5-HT takes into consideration the concomitant CNS effects of progestin administration. In contrast, OC-induced imbalance in cortical excitability is a mechanism that considers the dual effects of estradiol and progestin exposure and has growing theoretical support as alterations in cortical excitability (Smith et al., 2003) and abnormalities in cortical gamma-aminobutryic acid (GABA) concentrations have been demonstrated in women with PMDD (Epperson et al., 2002).

Estrogen, progesterone and cortical excitability

Unlike the genomic effects of estrogen which are mediated by nuclear estrogen receptors, estrogen's non-genomic effects are immediate and short-lived, occurring in seconds to minutes (Wong et al., 1996). These non-genomic actions of estrogen in the brain increase neuronal excitability (Wong et al., 1996) and lower the seizure threshold (Morrell, 1999; Woolley, 1999). Estrogen exerts its excitatory effects in some brain areas via two mechanisms – by reducing glutamic decarboxylase mRNA, which diminishes GABA-mediated inhibition (Murphy et al., 1998) and by acting as an agonist at the N-methyl-D-aspartate (NMDA) receptor (Gureviciene et al., 2003; Zamani et al., 2004), thereby increasing excitatory neurotransmitter action.

In contrast, progesterone administration is associated with enhanced neuronal inhibition and an elevation of the seizure threshold (Morell, 1999). These actions of progesterone are derived from its α-ring reduced metabolite 3α-hydroxy-5α-pregnan-20-one (allopregnanolone; ALLO). As mentioned, ALLO acts as an agonist at the $GABA_A$ receptor thereby increasing neuronal membrane conductance to Cl-, resulting in hyperpolarization of the membrane and reduced neuronal excitability (Majewska, 1987). Allopregnanolone's action is analogous to the sedative and analgesic actions of benzodiazepines and it produces anxiolytic-like behavioral effects in animal models (Bitran et al., 1991; Brot et al., 1997; Wieland et al., 1991). Other neurosteroids such as pregnanolone sulfate and dehydroepiandrosterone sulfate (DHEAS) are $GABA_A$ receptor antagonists, thereby reducing GABA mediated inhibition (Majewska et al., 1988; Majewska et al., 1990).

The role of neurosteroids in depression and PMDD

Given the excitatory effects of estrogen and the inhibitory, anxiety-reducing effects of ALLO, the role of these steroids and their metabolites in the pathophysiology of affective disorders has been given much attention. A study conducted by Schmidt et al. (1998) showed that women with PMDD react abnormally to normal levels of circulating sex steroids. The study involved administering leuprolide to suppress ovulation and then adding back estradiol and progesterone in healthy women and women with PMDD in a double-blind crossover design. Whereas the add-back estrogen and progesterone had no effect in the healthy controls, it led to a recurrence of sadness, anxiety, bloating, impaired function, and irritability in women with PMDD. The authors conclude that mood symptoms in women with PMS are ''an abnormal response to normal hormonal changes'' and this is now the prevailing theory for the origins of PMDD symptoms (Schmidt et al., 1998).

The mechanism by which these hormones exert these differential effects in women with PMDD as compared to healthy women may be related, at least in part, to a dysregulation of central ALLO production and/or altered GABAergic response to this potent agonist. Two studies found that women with PMDD have reduced luteal phase ALLO levels compared to controls (Monteleone et al., 2000; Rapkin et al., 1997), although this finding has not been confirmed in a number of other studies (Epperson et al., 2002; Girdler et al., 2001; Schmidt et al., 1994; Wang et al., 1996) and a reduction in PMS symptoms with selective serotonin reuptake inhibitor treatment correlated with lower allopregnanolone levels (Freeman et al., 2002). However, Wang and

colleagues (1996) found that in women with PMS, symptomatic cycles compared to asymptomatic cycles were characterized by lower ALLO levels and higher pregnenolone sulfate (PS) and estradiol levels during the luteal phase. The lower ALLO levels and higher estradiol and PS levels in women with PMS/PMDD may impair the ability to enhance GABA mediated inhibition during periods of enhanced steroid induced cortical excitation, such as that which may occur with late follicular estradiol production, and lead to the symptoms characteristic of the disorder. These apparent discrepancies between studies highlight the limitations of peripheral measures of ALLO. Moreover, preclinical studies indicate that peripheral measures of ALLO may not correlate with central levels, particularly during period of increased stress (Vallee et al., 2000).

Brain GABA concentrations, an indicator of cortical GABA neuronal function, is dysregulated in women with premenstrual dysphoric disorder (PMDD) (Epperson et al., 2002). Occipital cortex GABA concentrations as measured using proton magnetic resonance spectroscopy (1H-MRS) fluctuate in a phase and diagnosis-dependent fashion, with increases in GABA from the follicular to luteal phase in women with PMDD and a decrease in GABA from the follicular to luteal phase in healthy controls (Epperson et al., 2002). Providing collaborative evidence of alterations in cortical excitability in women with PMDD, Smith and colleagues (2003) employed transcranial magnetic stimulation (TMS), a technique that measures amplitude of muscle response following transcranial stimulation and uses a conditioning pulse below the threshold for muscle response to determine the relative strength of the excitatory and inhibitory inputs that the corticospinal neurons activate. Smith et al. found that women with PMDD showed relative facilitation in the luteal phase as compared to control subjects who showed more inhibition (Smith et al., 2003). These findings suggest that the higher progesterone (and presumably ALLO) levels that characterize the luteal phase fail to exert their inhibitory effects in women with PMDD. These findings are consistent with those of others who have noted a relative lack of sensitivity to the behavioral effects of administration of $GABA_A$ receptor agonists (benzodiazepines and pregnanolone) during the luteal phase in women with PMDD compared to healthy controls (Sundstrom et al., 1998). Taken together, these studies suggest that women with PMDD have abnormal GABAergic responses to either endogenous production or exogenous administration of $GABA_A$ receptor agonists during the luteal phase of the menstrual cycle.

OC and neurosteroid levels: background

Oral contraceptives introduce exogenous hormones into the body – ethinyl estradiol and some form of progestin. The dose of estrogen in OCs that are currently prescribed range from 20 to 50 μg of ethinyl estradiol (Petitti, 2003). Whereas ethinyl estradiol is the most commonly used estrogen, there are multiple progestins used in OC formulations. Many of today's OCs contain progestins that are derivatives of the hormone 19-nortestosterone. The earlier derivatives of 19-nortestosterone are called estranes and include derivatives of norethindrone such as norethindrone acetate, norethynodrel, and ethynodiol diacetate. A more recent class of compounds derived from 19-nortestosterone, the gonanes, includes norgestrel and its derivatives such as levonorgestrel (LNG), gestodene (GSD), desogestrel (DSG), and norgestimate (NGM). On the whole, the gonanes are more potent progestational agents than the estranes and with the exception of LNG, less androgenic than their estrane counterparts (Carr, 1998). An even newer progestin is a 17alpha-spironolactone derivative, drospirenone (DRSP), which possesses antimineralcorticoid and antiandrogenic activity (Fuhrmann et al., 1996). The dose of progestin used in OCs varies according to the potency of the progestin and the OC formulation. In monophasic preparations, the dose of progestin remains constant throughout the cycle. In contrast, biphasic and triphasic preparations are characterized by varying doses of the progestin component in order to mimic the fluctuations of progesterone during the menstrual cycle (Petitti, 2003).

To what extent do ethinyl estradiol and the progestin included in oral contraceptives affect levels of sex steroids, and by extension levels of neurosteroids? Research indicates that the ingestion of exogenous hormones suppresses the body's production of endogenous estrogen and progesterone, leading to a reduction in natural levels of these hormones (Lobo & Stanczyk, 1994). One significant factor, which may affect how synthetic progestins affect the CNS and mood is the nature and activity of their metabolites. One progestin, ethynodiol diacetate, which is structurally related to norethindrone (Lobo & Stanczyk, 1994), is metabolized to ALLO (Simic et al., 1998), a unique property that is not shared by other progestins. It is thus important to differentiate between different types of progestins and different OC preparations (i.e. monophasic, biphasic, and triphasic)

since it is likely that different compounds will exert varying effects on neurosteroid levels and that changes in progestin levels found in biphasic and triphasic preparations might affect neurosteroids differently than the constant levels of progestin found in monophasic preparations.

A final factor that must be taken into account when investigating the effects of OCs on neurosteroid levels and mood is the study population involved. As discussed above, research indicates that women with PMDD may have lower luteal phase levels of ALLO during symptomatic cycles compared to non-symptomatic cycles, reduced levels of cortical GABA in the follicular phase, and increased facilitation during the luteal phase. Thus, OC studies which fail to distinguish between healthy women and women with premenstrual symptoms obscure potential differences between how OCs affect healthy women and how OCs affect women with a predisposition to mood fluctuations. It is possible that the same OC formulation will exert differential effects on healthy women and women with premenstrual symptoms prior to beginning OC use.

OCs and neurosteroid levels – healthy women

Two studies directly investigate the relationship between OC use and neurosteroid levels. One study conducted by Follesa et al. (2002) investigated the effects of OCs on the concentrations of pregnanolone, progesterone, and allopregnanolone in rats and women. Rats were given a combination of 0.030 mg ethynyl-estradiol and 0.125 mg levonorgestrel (EE-LNG) for 6 weeks and women were given EE-LNG (30 mg and 125 mg, respectively) for 3 months. Concentrations of progesterone and its metabolites were consistently reduced in the rats' cerebral cortexes after OC administration. Pregnenolone was reduced by 41%, progesterone by 74%, and allopregnanolone by 79%. Plasma concentrations were also reduced but to a lesser degree. In humans, the elevation in neurosteroid levels that occurred in the luteal phase before OC treatment was completely abolished after three months of OC treatment. Neurosteroid levels measured on day 18 after the onset of the third OC cycle were all lower than the neurosteroid levels measured on day 7 (follicular) of women's menstrual cycles prior to OC use. The study measured potential behavioral correlates of these reduced neurosteroid levels and found that rats treated with OCs exhibited an anxiety-like behavioral profile in the plus-maze test. The study also measured changes in receptor structure and gene expression and found that rats treated with OCs showed an increase in the $GABA_A$ receptor $\gamma 2L$ and $\gamma 2S$ subunit mRNAs, which could represent a plastic adaptation of $GABA_A$ receptor gene expression to the lower levels of neurosteroids. The investigators proposed that OCs have a direct effect on the brain since ovariectomy of rats did not change the effect of OCs on the neurosteroid concentrations in the cerebral cortex and on the $GABA_A$ receptor gene expression. This observation, coupled with the finding that the decrease in progesterone and allopregnanolone in the rat cerebral cortex following OC administration was more dramatic than the decrease in these steroids in rat plasma, led to the conclusion that "the EE-LNG combination might ... directly affect the synthesis and accumulation of these steroid hormones in the brain." One proposed mechanism for this effect is that OCs regulate the activity or expression of enzymes that catalyze the synthesis of neurosteroids. As measures of behavioral and mood correlates of the reduced neurosteroid levels in the women taking OCs were not obtained, one can only suggest that based on the animal behavior data, women on EE-LNG could experience periods of heightened anxiety. Whether synthetic progestin suppression of the anxiolytic effects of natural progesterone could lead to negative mood changes, particularly in the face of estrogen administration, waits to be confirmed in humans.

Paoletti et al. (2004) investigated whether an oral contraceptive formulation containing 30 μg ethinyl estradiol and 3 mg of drospirenone (EE/DRSP) affected psychological symptoms and neurosteroid levels in healthy women. These investigators compared OC users with healthy, menstruating women not taking OCs and found that in the control group, progesterone, ALLO, and 3α, 21-dihydroxy-5α-pregnan-20-one (THDOC) values were higher in the luteal phase than in the follicular phase and that this difference was preserved into the third cycle. In the OC group, the levels of progesterone, ALLO, and THDOC were reduced in the luteal phase of the third cycle of OC treatment. The SCL-90 score, a measure of anxiety, depression, obsessive-compulsive tendencies, and other psychiatric symptoms, was also reduced in the OC group by the third cycle. Finally, the level of DHEAS, a neurosteroid that acts as an antagonist at the $GABA_A$ receptor (Majewska et al., 1990), was reduced in the OC group by the third cycle.

Based on the findings that women on EE/DRSP show less anxiety after three cycles of OC use, Paoletti et al. conclude that the lower levels of DHEAS in the OC

group may explain the reduced anxiety. They argue that DHEAS exerts an anxiety-inducing effect due to its antagonist actions at the $GABA_A$ receptor and correlate the low levels of DHEAS with the reduced anxiety in the OC group. In addition to the $GABA_A$ antagonistic properties of DHEAS, DHEAS also potentiates neuronal NMDA response (Bergeron et al., 1996; Monnet et al., 1995). The excitatory effect of DHEAS, along with the finding that lower levels of DHEAS are correlated with lower anxiety, further suggests that an alteration in cortical excitability may be one mechanism by which OCs alter mood.

In summary, two studies have found that three cycles of OC use lead to lower levels of plasma progesterone and ALLO (Follesa et al., 2002; Paoletti et al., 2004). Despite documenting a decline in potent $GABA_A$ receptor agonists, one of the studies found that anxiety levels were reduced with OC use. The investigators proposed that this behavioral finding may be attributed to reductions in DHEAS levels, which were included in their battery of steroid assays. Other studies in the literature suggest that OC administration is associated with decreases in serum DHEAS levels (see Carlstrom et al., 2002 for a listing of this literature). Thus, while EE-LNG reduces levels of anxiolytic neurosteroids and increases anxiety-like behavior in rats, EE/DRSP, which also reduces levels of anxiolytic neurosteroids, leads to lower levels of anxiety in women perhaps due to its ability to lower DHEAS levels. It is not yet clear whether these results can be generalized to other OCs.

To our knowledge, Follesa et al. and Paoletti et al.'s studies are the only findings to date that directly measure the relationship between OCs, neurosteroids, and mood. Yet one can look at studies conducted on the effects of OCs and mood and see if the findings are consistent. There are numerous studies that have been conducted on the relationship between OCs and mood (see review article by Oinonen & Mazmanian, 2002) but many studies do not control for the type of OC used or distinguish between healthy subjects and subjects with premenstrual symptoms, two factors which, as explicated above, are crucial in understanding the effects of OCs on mood. Thus, instead of reviewing all studies that have been conducted to date on the relationship between mood and OCs, this paper will review studies that specify the OC formulation used and whether the study population includes healthy women, women with premenstrual symptoms, or both. The studies discussed below use the more recently derived progestins (the norgestrel derivatives and DRSP) since these make up most OCs currently on the market and possess novel properties that distinguish them from older progestins.

The overwhelming number of the studies that have been conducted to date on the relationship between newer OCs and mood have found that OCs have a positive effect on mood and general well-being, though many of these studies do not include a control group. (See Table 1 for a listing of studies that use a single OC.) For instance, Egarter et al. and Ernst et al. investigated an OC containing EE/DSG in first-time users for 4 and 3 treatment cycles, respectively. The former study found an improvement in overall quality of life with mood being one subscale on which improvement was reported (Egarter et al., 1999). In the latter study, 71% of participants reported increased mood and 62% of participants reported an improvement in nervousness (Ernst et al., 2002). Deijen et al. conducted a study using an OC with GSD and found that those who switched from another OC preparation improved on measures of depression, moodiness, anxiety, and anger though first-time users did not experience any change from baseline (Deijen et al., 1992). This study included a control group not taking any OC, which like the fist-time users, did not experience any change from baseline. Rosenthal et al. used an OC containing LNG in their study of adolescents' attitudes to oral contraceptives and found that despite expectations of negative mood changes, 91% of participants did not experience negative mood changes (Rosenthal et al., 2002). The same OC was used by Wimberly et al. who found that the mood changes reported by study participants could, at least in part, be explained by participants' anticipation of mood changes (Wimberly et al., 2002).

Similar results are found in studies that investigate DRSP, a progestin that is not derived from 19-nortestosterone but from spironolactone. Two studies found that after six treatment cycles of EE/DRSP, participants experienced a significant reduction in negative affect score (Brown et al., 2001; Parsey & Pong, 2000). Brown et al.'s study saw this reduction in negative affect in the premenstrual and menstrual phases while Parsey and Pong found this improvement in all menstrual phases. A third study compared an extended cycle of EE/DRSP with a 21-day regimen of the same formulation and found that after 6 months, 85% of the subjects on the extended regimen and 66% of subjects on the 21-day regimen felt better as compared to baseline (Sillem et al., 2003).

Table 1. Summary of studies investigating the relationship between OCs and mood in which a specific OC formulation was used

Study	Progestin used	Subjects	Duration of OC use	Outcome	Strengths/weaknesses of study
Sillem et al., 2003	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	1,221 women on a 21-day regimen with 7-day pill free period and 175 women on an extended regimen (varying from 42 to 126 days)	6 treatment cycles used for study measures	85% of subjects on the extended regimen felt better than at the beginning and 2% worse after 6 months. Of the women on the 21-day regimen, 66% of women felt better and 3% worse.	1. *Compared extended cycle to 21-day cycle*. 2. Not placebo controlled. 3. No daily prospective ratings. 4. Subjects not asked about premenstrual syndrome history before beginning study. 5. General satisfaction, not specific symptoms, was measured.
Ernst et al., 2002	DSG (20 μg ethinyl estradiol and 150 μg DSG)	3,677 first-time OC users completed study	3 treatment cycles	All subscales of the Q-LES-Q, including mood, showed a statistically significant increase after cycle 3 as compared to baseline. Of those who reported depressed mood at baseline, 71% reported improvement after OC treatment. 62% reported improvement in nervousness.	1. *Very large sample size*. 2. Not placebo controlled. 3. Subjects not asked about premenstrual syndrome history before beginning study. 4. No prospective daily ratings.
Rosenthal, et al., 2002	LNG (20 μg ethinyl estradiol and 100 μg LNG)	43 female adolescents (36 completers)	6 treatment cycles	65% of subjects anticipated worsening of mood changes. At six months, 91% of subjects had *not* experienced negative mood changes. 97% of participants were generally satisfied with this OC.	1. *Measured anticipation of mood changes which might affect actual experience of mood*. 2. Not placebo controlled. 3. No daily prospective ratings of mood. 4. Subjects not asked about premenstrual syndrome history before beginning study.
Wimberly et al., 2002	LNG (20 μg ethinyl estradiol and 100 μg LNG)	169 women completed study	3 treatment cycles	20% of participants anticipated mood changes and 26% of participants reported mood changes after 3 treatment cycles. This correlation is more than would be expected by chance. On the whole, 90% of users were satisfied with this OC combination.	1. *Measured anticipation of mood changes which might affect actual experience of mood*. 2. Not placebo controlled. 3. No daily prospective ratings. 4. Subjects not asked about premenstrual syndrome history before beginning study.
Brown et al., 2001	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	322 healthy women	6 treatment cycles	Significant reduction in premenstrual and menstrual scores of negative affect and water retention as measured by the WHAQ. There was no significant difference between new users and women who switched from other OCs.	1. Not placebo controlled. 2. No daily prospective ratings. 3. Subjects not asked about premenstrual syndrome history before beginning study.
Parsey and Pong, 2000	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	220 healthy women completed study	13 treatment cycles (6 cycles used in PMS measurements)	Water retention and negative affect improved in all menstrual phases from baseline to cycle 6. No changes found for well-being, impaired concentration, or weight as measured by the MDQ.	1. Not placebo controlled. 2. No daily prospective ratings. 3. Subjects not asked about premenstrual syndrome history before beginning study.

(*continued*)

Table 1 (*continued*)

Study	Progestin used	Subjects	Duration of OC use	Outcome	Strengths/weaknesses of study
Egarter et al., 1999	DSG (20 μg ethinyl estradiol and 150 μg DSG)	604 first-time users completed study	4 treatment cycles	The total quality of life score as measured by the Q-LES-Q showed a highly significant increase at cycle 4 as compared to baseline. Mood was one of the subscales on which an increase was seen.	1. Not placebo controlled. 2. Subjects not asked about premenstrual syndrome history before beginning study. 3. No prospective daily ratings.
Deijen et al., 1992	GSD (30 μg ethinyl estradiol and 75 μg GSD)	200 first-time OC users, 370 switchers from other OCs, 140 non-users (13 dropped out)	3 treatment cycles	Switchers improved on measures of depression, moodiness, anxiety, and anger after using new OC as measured by AMQ. Similar improvements also measured by the SIP. Neither first-time OC users nor control group experienced any change from baseline.	1. *Control group of non-OC users.* 2. Not placebo controlled. 3. No daily prospective ratings. 4. Subjects not asked about premenstrual syndrome history before beginning study. 5. Switchers might have self-selected as those unhappy with old OC (given their higher baseline scores on negative mood measures) and thus not a group of random switchers.

Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire); AMQ (Amsterdam Mood Questionnaire); SIP (Sickness Impact Profile); PGWBI (Psychological General Well-Being Index); Moos Menstrual Distress Questionnaire (MDQ); WHAQ (Women's Health Assessment Questionnaire).

Studies have also been conducted that compare two or three types of OCs, varying the type of progestin used and/or the doses of the progestin (e.g. a monophasic preparation vs. a triphasic preparation). (See Table 2 for a listing of studies that compare multiple OCs.) One study comparing LNG and DSG found that both OCs caused a decrease in PMS symptoms after 6 treatment cycles but there were no clinically significant changes in quality of life between baseline and post-treatment (Winkler et al., 2004). A second study compared DRSP and LNG and found that after six months, the prevalence of PMS symptoms during the premenstrual phase was significantly lower in the DRSP group (Sangthawan & Taneepanichskul, 2005). Foidart et al. compared DRSP and DSG and did not find a statistical difference between the two groups, though they did find PMS symptoms lower in the DRSP group after treatment despite a higher incidence of PMS symptoms in the DSG group before treatment (Foidart et al., 2000). A fourth study compared monophasic GSD, triphasic GSD, and monophasic DSG and found that improvement in well-being was significant at cycles 6 and 9 for the triphasic GSD group and at cycle 13 for the DSG groups. Negative affect and arousal showed a significant decrease from baseline for 2 or more cycles in all 3 groups (Bruni et al., 2000). Finally, a study comparing monophasic LNG, triphasic LNG, and non-OC users showed that OC users showed less variation for sadness/depression ratings over the course of the menstrual cycle. Furthermore, non-OC users showed a sharp premenstrual increase in sadness/depression that was not seen in the OC groups (Abraham et al., 2003). This study is significant in that participants were taking the study OCs for at least three months before beginning the study ratings, thus minimizing the possibility that the study's findings are merely side effects of a new OC or a placebo reaction to a pill (Abraham et al., 2003).

Emerging from the review of these studies is that contrary to popular belief that OCs exacerbate PMS symptoms or lead to a worsening of mood, most studies find that OCs containing newer progestins have beneficial effects on mood. It is possible that although OCs are lowering anxiolytic neurosteroid levels, they are compensating for this reduction in another way, perhaps by lowering anxiety-provoking neurosteroid levels such as DHEAS as was shown in Paoletti's study. Until more studies directly measure the effect of OCs on neurosteroid levels and corresponding changes in mood it is hard to determine the underlying mechanism of these observed mood changes, but specifying the progestin used and grouping studies by hormonal formulations is the first step towards unraveling the relationship between hormones, OCs, and mood.

Table 2. Summary of studies comparing the effects of multiple progestins on mood

Study	OCs used	Subjects	Duration of OC use	Outcome	Strengths/weaknesses of study
Sangthawan and Taneepanichskul, 2005	EE/LNG and EE/DRSP	99 women completed study	6 treatment cycles	At baseline, the prevalence of PMS symptoms was not statistically different between the two groups as measured by the WHAQ. After six months, the prevalence of PMS symptoms such as irritability, anxiety, and feeling sad or blue during the premenstrual phase was significantly lower in DRSP/EE group as compared to the LNG/EE group.	1. *Randomized, comparative study.* 2. *Prevalence of premenstrual symptoms at baseline assessed* but not confirmed with prospective ratings. 3. Women with PMS symptoms at baseline not grouped separately from healthy women. 4. Not placebo controlled. 5. No daily prospective ratings of mood during OC use.
Winkler et al., 2004	EE/DSG and EE/LNG	788 women completed study	6 treatment cycles	PMS symptoms decreased in both groups. No differences between the groups for mean scores on PGWBI or POMS at all time points. No clinically significant changes in quality of life between baseline and post-treatment.	1. *Group-comparative, randomized, multi-center trial.* 2. *PMS symptoms assessed at baseline although not confirmed with daily ratings.* 3. Not placebo controlled. 4. No daily prospective ratings of mood during OC use but did rate at baseline, and cycles 1, 3, and 6.
Abraham et al., 2003	Monophasic LNG triphasic LNG Non-OC users	Data used from 119 healthy women	At least 2 cycles. Women had been on OCs for at least 3 mos. before beginning study	All three groups showed cyclic changes in general ''premenstrual syndrome-like'' symptoms and at least two mood ratings. OC groups had less variation for sadness/depression and non-OC group showed sharp premenstrual increase in sadness/depression as compared to OC groups.	1. *Control group of non-OC users.* 2. *Daily prospective ratings of mood.* 3. *Women had already been on OCs before enrolling in study. Study results are not side effects from first few months of use.* 4. Not double-blind.
Foidart et al., 2000	EE/DRSP and EE/DSG	627 women completed study	26 treatment cycles	Before treatment, PMS symptoms were higher in EE/DRSP group than in the EE/DSG group but lower during treatment. The difference was not statistically significant before or after treatment.	1. *Comparison group with another OC.* 2. *Prior PMS symptoms were assessed* but using retrospective measures that were not confirmed with prospective ratings. 3. *Prospective assessment of PMS symptoms during OC use.* 4. Not placebo controlled.
Bruni et al., 2000	Monophasic GSD triphasic GSD monophasic DSG	2419 healthy women enrolled in study. Well-being data available for 1433 women at cycle 9 and 695 at cycle 13	13 treatment cycles	Improvement in well-being was significant at cycles 6 and 9 for the triphasic GSD group and at cycle 13 for the DSG group. No statistically significant differences among treatment groups in the overall well-being scores. Negative affect and arousal showed significant decrease from baseline for 2 or more cycles in all 3 groups.	1. *Comparison group with another OC.* 2. Not placebo controlled. 3. No daily prospective ratings of mood during OC use.

PGWBI (Psychological General Well-Being Index); POMS (Profile of Mood States); WHAQ (Women's Health Assessment Questionnaire).

OCs and neurosteroid levels – women with PMDD

The studies cited above measure PMS symptoms at baseline to compare baseline ratings to post-treatment ratings but they do not separate subjects into two groups – those with PMS symptoms and those without PMS symptoms. Some studies have been conducted that measure the effects of OCs on mood in women with a PMS or PMDD diagnosis. (See Table 3 for a listing of these studies.) A double-blind, placebo controlled study concluded that women with a history of premenstrual irritability have more adverse effects with estrogen dominated pills whereas women without a history of premenstrual irritability have more adverse effects with progesterone dominated pills (Cullberg, 1972). Yet these differences are nonsignificant and OCs did not significantly improve or worsen premenstrual mood as compared to placebo. Viewed in light of recent research on the relationship between neurosteroid levels, cortical excitability, and mood, it is possible that the women with premenstrual irritability react with enhanced negative affect to estrogen-dominated formulations as estrogen administration may exacerbate the underlying imbalance between cortical excitation and inhibition.

Bancroft et al. compared a triphasic and a monophasic OC, both containing L-norgestrel, a gonane derivative of 19-nortestosterone, and found that among women with PMS symptoms before taking the OC, those taking the triphasic preparation had more negative mood changes compared to those taking the monophasic preparation (Bancroft et al., 1987). Another study compared monophasic EE/DSG with monophasic and triphasic EE/LNG. All OCs used had a beneficial effect on PMS symptoms as compared to pre-treatment measurements but these effects only lasted for three treatment cycles. The monophasic DSG caused fewer negative symptoms than the other two preparations (Backstrom et al., 1992). Both of these studies find that triphasic preparations cause more negative mood changes than monophasic preparations. One possible explanation for this in light of the proposed theoretical model is that since women with PMDD may possess an underlying sensitivity to fluctuating hormone and neurosteroid levels, they may experience more negative mood changes when taking a triphasic preparation in which the level of progestin is fluctuating.

Graham and Sherwin investigated a triphasic OC containing norethindrone, an estrane derivative of 19-nortestosterone, in women with prospectively confirmed PMS. They found that as compared to placebo, the OC group did not show any beneficial effects with regard to mood symptoms (Graham & Sherwin, 1992). Yet both the OC and placebo groups showed a reduction in depression scores in the premenstrual phase (Graham & Sherwin, 1993). Furthermore, when women were divided into subgroups based on prospective ratings at baseline, women who had been depressed at baseline and were taking the OC reported greater improvement premenstrually in impairment at work, needing sleep, and lack of energy (1992).

Recent research on the use of Yasmin (EE and DRSP) to treat PMDD has indicated a potential therapeutic effect of this particular OC. Apter et al. (2003) found that EE/DRSP improved general well-being after 6 treatment cycles in women reporting minor PMS symptoms. A second study found that negative affect improved significantly from baseline after two cycles of EE/DRSP. This study included women with and without self-reported PMS and found no differences between the two groups in their positive response to the OC (Borenstein et al., 2003). Neither of these two studies was double-blind or placebo-controlled and the latter study did not confirm self-reported PMS symptoms with any objective measures. Freeman et al. (2001) included 82 women in a double-blind placebo-controlled study. All subjects were diagnosed with PMDD according to DSM-IV criteria and were randomized to receive either EE/DRSP or placebo. After three treatment cycles the EE/DRSP group showed a 10% greater change from baseline compared to the placebo group for Factor 1, which included mood swings, anger, irritability, sensitivity, crying, anxiety, desire to be alone, and depressed mood. This study found a high placebo response rate of 43% that did not disappear after the first treatment cycle and it did not include a placebo run-in cycle to exclude placebo responders. Yet despite these limitations, this study does present initial evidence that EE/DRSP is a more effective treatment than placebo for some symptoms experienced by women with PMDD.

One potential mechanism by which EE/DRSP may exert beneficial effects in women with PMDD is by lowering DHEAS levels, leading to an increase in cortical inhibition. In addition, drospirenone has antiandrogenic activity that is five to ten times higher than that of progesterone (Fuhrmann et al., 1996). This quality of drospirenone and other newer progestins such as DSG and GSD is relevant to the study of OCs and mood in light of recent studies on the role of androgens in premenstrual dysphoric disorder. One study found that serum testosterone levels are elevated in women with

Table 3. Summary of studies investigating the relationship between OCs and mood in women with PMS symptoms

Study	OC used	Subjects	Duration of OC use	Outcome	Strengths/weaknesses of study
Apter et al., 2003	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	336 women reporting minor PMS during prescreening (261 completed study)	6 treatment cycles	All subscale scores on the PGWBI improved significantly from baseline at cycles 3 and 6. Change from baseline for the subscales of vitality, anxiety, and positive well-being were particularly robust.	1. *PMS history taken for 3 cycles prior to screening. At least one somatic and 1 psychological symptom needed in 2 of 3 cycles*. 2. Not placebo controlled. 3. No daily prospective ratings during OC use.
Borenstein et al., 2003	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	Data used from 858 women (72.3% with self-reported PMS)	2 treatment cycles	All individual items on the MDQ improved significantly in the premenstrual and menstrual phase. Negative affect improved significantly from baseline in all phases of the menstrual cycle. No distinction in results between those who were treated for PMS prior to study and those who were not.	1. No confirmation of reported PMS symptoms with prospective daily ratings. 2. Not placebo controlled. 3. No daily prospective ratings of mood.
Freeman et al., 2001	DRSP (30 μg ethinyl estradiol and 3 mg DRSP)	82 women with diagnosed PMDD according to criteria in DSM-IV completed study	3 treatment cycles	DRSP/EE significantly better than placebo at reducing PMS symptoms of increased appetite, food cravings, acne, desire to be alone, hot flushes. DRSP/EE group showed a 10% greater change from baseline compared to the placebo group for Factor 1, which includes mood swings, anger, irritability, sensitivity, crying, anxiety, and depressed mood.	1. *Double-blind, placebo controlled study.* 2. *PMDD confirmed with daily prospective ratings using the COPE*. 3. Small sample size – not large enough to detect significant differences between active and placebo groups. 4. High placebo response rate of 43%.
Graham and Sherwin, 1993	Triphasic EE/ norethindrone	45 women with moderate to severe PMS completed study	One baseline cycle, 3 treatment cycles	By 3rd treatment cycle, cyclicity of mood throughout menstrual cycle was no longer apparent. In premenstrual phase, there was a significant reduction in depression scores for both the OC and placebo groups. This effect was dissociated from any change in sexual interest.	1. *Double-blind, placebo controlled trial*. 2. *Subjects all had complaints of moderate to severe PMS which was prospectively confirmed*. 3. *Daily prospective ratings of mood during treatment phase*.
Graham and Sherwin, 1992	Triphasic EE/ norethindrone	45 women with moderate to severe PMS completed study	One baseline cycle, 3 treatment cycles	As compared to placebo, the OC did not show any beneficial effects with regard to mood symptoms. Yet when women were divided into subgroups based on prospective ratings at baseline, women who had been depressed at baseline and were taking the OC reported greater improvement premenstrually in impairment at work, needing sleep, and lack of energy.	1. *Double-blind, placebo controlled trial*. 2. *Subjects all had complaints of moderate to severe PMS which was prospectively confirmed*. 3. *Daily prospective ratings of mood during treatment phase*.

(*continued*)

Table 3 (*continued*)

Study	OC used	Subjects	Duration of OC use	Outcome	Strengths/weaknesses of study
Backstrom et al., 1992	Monophasic EE/DSG compared with monophasic and triphasic EE/LNG	37 women completed study. Some with PMS (mood changes only in premenstrual phase) and some with PMA (premenstrual aggravation of mood changes)	4 treatment cycles, 2 on each OC	All OCs had beneficial effect on PMS symptoms as compared to pre-treatment measurements as measured by a daily rating scale. Only lasted for first three treatment cycles and effect no longer present by cycle 4. The monophasic DSG pill caused less mood changes than the monophasic and triphasic LNG pill.	1. *Double-blind, cross-over design.* 2. *Comparison between different OCs and different formulations.* 3. *Daily prospective ratings of mood.* 4. *Women classified as having PMS or PMA before beginning treatment using prospective ratings.* 5. Not placebo controlled.
Bancroft et al., 1987	L-norgestrel. Monophasic (150 μg L-norgestrel) and triphasic (L-Norgestrel varying from 50 μg to 125 μg)	Data used from 19 women taking triphasic pill; 18 women taking monophasic. Some with PMS symptoms	2 treatment cycles	Of those women with high premenstrual mood scores before taking the pill (i.e. negative mood), those taking the triphasic preparation had a worsening of mood compared to those taking the monophasic preparation. Negative mood evident in middle of cycle when progestin levels are increasing (but are still lower than levels in monophasic preparation).	1. *Daily diary of symptoms.* 2. *Subjects classified as having history of premenstrual mood before beginning OC use.* 3. Not placebo controlled.
Cullberg, 1972	EE/Norgestrel. Norgestrel in varying doses ranging from 0.06 mg-1.0 mg	320 women, 80 in each of 4 groups. 23 women dropped out	2 treatment cycles	Women with a history of premenstrual irritability had more adverse effects with estrogen dominated pills whereas women without a history of premenstrual irritability had more adverse effects with progesterone dominated pills. These differences were statistically nonsignificant and OCs did not significantly improve or worsen premenstrual mood as compared to placebo.	1. *Double-blind, placebo controlled study.* 2. *Premenstrual symptom background obtained at baseline and subjects classified by premenstrual history in data analysis.* 3. Sample size not large enough to detect statistical significance.

COPE (Calendar of Premenstrual Experiences Scale); PGWBI (Psychological General Well-Being Index); Moos Menstrual Distress Questionnaire (MDQ).

PMS symptoms as compared to controls during the luteal phase (Eriksson et al., 1992). Given the connection between androgenicity and mood, the antiandrogenic effects of some progestins such as DRSP may lead to differential effects on mood.

Areas for future research

Follesa et al. and Paoletti et al.'s studies provide a model that should be replicated in future studies. Both investigations measure levels of progesterone and its metabolites before and after OC treatment. Furthermore, both include behavioral measures that can then be correlated positively or negatively with the biological effects of OC treatment. Future research should incorporate these methods as well as expand upon them. A similar design may be employed to study the effects of other types of OCs on neurosteroid levels such as allopregnanolone, GABA, THDOC, and DHEAS. It might also be interesting to compare neurosteroid levels in women on two different types of OCs and then to compare both groups to placebo. In addition to investigating gonane

derivatives and drospirenone, researchers might also wish to use an OC containing ethynodiol diacetate in studies of OC and neurosteroid levels since this particular progestin is converted to ALLO (Simic et al., 1998).

In addition to looking at the effects of OCs on neurosteroid levels in healthy women, neurosteroid levels should also be studied in women with prospectively confirmed PMDD before and after OC treatment. Given the different ways in which women with PMDD respond to normal levels of circulating hormones (Schmidt et al., 1998), it would be interesting to compare neurosteroid levels of women with PMDD on OCs with neurosteroid levels of healthy women on OCs.

Future investigations should also begin to incorporate other available technology such as rapid transcranial magnetic stimulation to measure cortical inhibition and facilitation, H-MRS to measure amino acid neurotransmitter levels and fMRI to examine OC-related alterations in brain activation.

Finally, an area that warrants further research in the field of OCs and mood is the effect of extended cycle regimens of OCs on mood. Most of the studies that investigate the effects of OCs on mood involve OC use for three weeks and then a hormone-free week during which time withdrawal bleeding generally occurs. One study found that negative mood symptoms were worse during the 7-day hormone-free interval as compared to the 21 days of hormone-containing pills and the authors therefore recommend an extended cycle for women who experience negative mood symptoms while on OCs (Sulak et al., 2000). Recently, a new OC regimen has been approved that involves continuous hormone dosing with the exception of four withdrawal weeks per year (Seasonale,® Barr Laboratories, Pomona, NY). This new OC regimen was developed and marketed for the convenience of women (Anderson et al., 2003), but without knowledge of the CNS impact of extended daily exposure to estrogens and progestins. While it is still primarily a theoretical concern in humans, findings from rodent studies strongly suggest that daily exposure to estrogen results in a downregulation of estrogen receptors and a reduction in the neuroprotective profile of the hormone (Brown et al., 1996; Wise, 2001). The CNS effects of daily use of both an estrogen and a progestin for extended periods has not been well-elucidated in menopausal women undergoing hormone therapy or in young premenopasual women. Comparing the effects of monthly withdrawal versus less frequent hormone-withdrawal on neurosteroid levels and cortical excitability would yield interesting information about the value of a withdrawal week from a biological perspective and the potential positive and negative aspects of extending hormone use beyond three weeks without a withdrawal period.

Furthermore, extended cycle regimens could provide novel information on the relationship between OCs and mood. Most studies that investigate the relationship between OC use and mood look at three phases – premenstrual, menstrual, and postmenstrual. These phases are compared to the actual phases of the menstrual cycle with the premenstrual phase corresponding to the luteal phase, the menstrual phase corresponding to menstruation, and the postmenstrual phase representing the follicular phase. Yet from the perspective of hormone levels, the week before withdrawal bleeding is not identical to the luteal phase of a natural menstrual cycle, withdrawal bleeding is not equivalent to menstruation, and the ''postmenstrual'' phase in a woman on OCs is not identical to the follicular phase. It is very likely that women on OCs view the week before withdrawal bleeding as their luteal phase; women's expectations and associations with menstruation might affect their psychological experience in the premenstrual phase. This is also true of the withdrawal bleeding period. By employing an extended cycle regimen and eliminating the ''menstrual'' week, researchers will be able to study the hormonal effects on mood independent of the potential psychological effects of having or knowing that one is about to have a period. The third week of the first treatment cycle in an extended regimen will be identical to the third week of the first treatment cycle in a traditional regimen, but in the latter case it is also the ''premenstrual'' week. Extended cycle regimens allow researchers to divorce hormone levels from actual menstruation and thus measure the effects of hormones on mood without having to factor out the psychological effects of bleeding or the anticipation thereof.

Conclusion

Given the role of neurosteroid levels in the etiology of mood disorders and the effects of estrogen and ALLO on cortical excitability, there seems to be much need for further research into how OCs, which introduce exogenous sex steroids into the body, affect neurosteroid levels and the balance between cortical excitation and inhibition. This research must look at both healthy women and women with PMDD and must distinguish between different types of progestins. Findings of these studies could potentially help uncover the mechanism (or mechanisms) by which OCs influence mood in some healthy women and those with PMDD.

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