How does oral contraception affect mood?

NICOLA PLUCHINO, ANNA CARUSO, DIANA DAINO

Abstract

Some women experience oral contraception (OC) related increase in negative affect/mood. It may suggest that individual difference variables predispose certain women to specific OC-mediated changes in mood or affect. Only a few studies have examined specific individual difference variables that may increase the likelihood of OC-mediated changes in affect. Furthermore, very few of the studies were conducted using the low-dose OCs that are currently in use. The fact that synthetic sex steroids affect brain excitability and neurosteroidogenesis differentially, might be crucial to understand pharmacological causes of mood changes in women undergoing OC.

Key words: oral contraception, mood, sex, steroids

Introduction

Combined oral contraceptive (COC) pill is the most common type of contraception among young women, with user frequencies in Sweden of almost 56% within the ages of 18-24 and 29% in ages 25-34 [1]. Increased irritability, mood swings and depressive symptoms have always, in spite of decreasing hormone concentrations over time, been major reasons for discontinuing treatment [2-4]. When studied prospectively, 7% of women on COC report increased anxiety and 10% report increased depressive mood [5], whereas retrospective studies display somewhat higher rates of adverse mood effects [6]. Discontinuation rates due to adverse mood symptoms have been reported to be 14-21% among COC users, with the highest mood-related discontinuation rate in the oldest age group [7]. As many women refrain from using safe contraception because of adverse mood effects when on COCs, it is important to elucidate the underlying causes for these changes in affect. It can be assumed that not only the active ingredients, ethinylestradiol and progestins, in the oral contraceptive pill will affect the psychological experiences and adverse effects of treatment, but also psychiatric history, personality traits, interpersonal relationships and socioeconomic factors. Thus far, most efforts to elucidate these issues have relied on retrospective collection of data. A previous depressive episode is significantly associated with worsening of mood during COC, whereas prior dysmenorrhea and early onset of premenstrual syndrome are associated with improved mood [6]. The possibility that certain personality traits render subjects vulnerable to experience adverse mood symptoms, or may increase the likelihood of reporting adverse mood while on COC has thus far not been explored. High levels of personality traits of neuroticism, introversion, interpersonal dependency and lack of self-confidence have all been proposed to be risk factors for the development of depression [8-10]. Because prior depression is associated with adverse mood symptoms on COC, it is plausible that these personality traits are also associated with development or reporting of negative mood changes during COC use.

Risk factors to mood change

The fact that some women do experience OC-related increases in negative affect/mood suggests that individual difference variables predispose certain women to specific OC-mediated changes in mood or affect. The majority of research on such variables has focused on OC-related changes in mood or depression. Only a few studies have examined specific individual difference variables that may increase the likelihood of OC-mediated changes in affect. Furthermore, very few of the studies were conducted using the low-dose OCs that are currently in use.

Previous studies suggest that the following variables increase a woman’s risk of becoming depressed or exhibiting depressive symptoms when taking OCs:
(a) a history of depression;
(b) a history of moderate to severe "premenstrual depression" or severe premenstrual weepiness prior to OC use;
(c) a history of dysmenorrhea prior to OC use;
(d) a history of depression during or after pregnancy;
(e) a family history of OC-related depressive symptoms;
(f) a predisposition to a vitamin B 6 deficiency while taking OCs, and...
(g) a high level of psychological distress prior to OC use. While one study found that a history of psychological distress was not associated with an increase in symptoms of depression, this study only examined the first 2 months of OC use.

Two studies suggest that the following variables are unrelated to the development of depression while taking OCs: age; age at menarche; length of menstrual cycle; parental separation, divorce, or death; birth weight; feeding problems or serious illness during the first year of life; education; religion; and family size. Only four studies have investigated individual difference variables that predispose women to OC-related changes in affect. Women younger than 20 experienced more negative affect, or perhaps less positive affect, during days 13-18 of OC use than older women. This is in line with the finding that women older than 30 experience less tension than non-users during menstruation while taking OCs. Therefore, while women under age 20 are more likely to experience an increase in negative affect, women over 30 experience a decrease in negative affect. Another study found that women who are premenstrually ‘depressed’ at baseline show greater improvement in symptoms of depression, this study only examined the first 2 months of OC use.

A final study examined the following variables and found that they could not account for the observed differences in negative affect variability between monophasic OC users and non-users: age at menarche, reaction to menarche, mother’s attitude to menstruation, amount of preparation for menstruation, degree of menstrual discomfort during teens, and prior expectations about the effects of OCs on mood [2].

As well as the individual difference variables noted above, there are a number of OC-related variables that may affect women directly or interact with other variables to influence mood or affect. For example, OCs can differ in terms of constituents (types of estrogen and progesterone), dosage, ratio of progesterone to estrogen, and temporal pattern of dosage (monophasic, biphasic, or triphasic). A number of these variables have been investigated in terms of their effects on mood and a few in terms of their effects on affect [2].

**Progestins for contraception: mood-acting compounds**

The CNS steroid concentration results from the hormones, produced by peripheral glands, that cross the Blood-Brain Barrier, and from an autonomous production by the CNS. In fact, neurons and glia cells possess all the enzymes necessary for progesterone (P), testosterone and estradiol metabolism (aromatase, 5α-reductase mainly in neurons, 3α-hydroxysteroid dehydrogenase mainly in type 1 astrocytes). Neurons and glia cells coordinately metabolize steroid hormones, thus forming a functional unit; as both the endocrine glands and the local metabolism contribute to the pool of steroids present in the nervous tissues and the age-dependent changes in circulating levels of steroid hormones might reflect changes in brain levels. Moreover, the CNS itself is able to produce steroids from cholesterol, at least partially independent from the peripheral gland steroid secretion. The brain-produced steroids are called “neurosteroids” and exert important regulatory actions on neurons and glia cells.

In particular, one of the most important neurometabolite deriving from P is AP (3α, 5α-tetrahydroxyprogesterone) which major sources of circulating levels are gonads and adrenal cortex, and the central nervous system AP acts as an agonist of the γ-aminobutyric acid A (GABA-A) receptor; and it is involved in the regulation of stress, mood and behaviour with anxiolytic, sedative and antiepileptic effects. In fact, AP brain levels increase during acute stress, pregnancy, antidepressant and anxiogenic drugs; on the opposite, they decrease during chronic stress, parturition and depression. Ovarian steroids may influence circulating levels of AP. It has been reported that, in rats, circulating levels of AP fluctuate depending on the hormonal phase (higher on proestrus than on diestrous or estrous); moreover, ovariectomy significantly decrease AP levels both on periphery and in the CNS. On the other hand, the administration of 17β-estradiol restores the AP contents in particular in hippocampus, hypothalamus, pituitary gland and serum. Even P is able to increase AP levels in parietal lobe, hippocampus, hypothalamus and anterior pituitary in a dose-dependant manner. This increase in AP content in blood and cortical areas, correlated to P administration, is probably responsible for the anxiolytic effect of this compound. It has been recently described that brain AP concentration is higher in animals receiving a combination of estradiol benzoate (EB) plus P, than in those treated with EB alone or EB plus P in combination with an inhibitor of 5α-reductase or P metabolism. The positive effect on AP levels of the combined therapy EB+P may be due to the estrogen capacity to modulate the 5α-reductase and 3α-hydroxysteroid dehydrogenase (5α-R-3α-HSD) and on the higher availability of the P substrate for the metabolization into AP. Therefore, it is feasible
that even in women after menopause, the decrease of AP might be involved in the physiopathology of climacteric symptoms and P administration might play a beneficial role on brain biology.

In addition to aforementioned 5α-pregnane metabolites, P can be directly metabolized to 4-pregnen-3α-ol-20-one (3aHP) and to 4-pregnen-20α-ol-3-one (20αHP), catalyzed by the actions of 3α-HSO and 20αHSO respectively. These metabolic pathways were demonstrated in the pituitary and the hypothalamus. In addition to analgesic and anxiolytic effects by interaction with the GABA-A receptor complex, 3αHP regulates pituitary FSH secretion by rapid non-genomic interaction with the Ca-driven cell signaling mechanisms.

**Differential effects of oral progestins on AP content**

Natural P, when given orally, is highly vulnerable to enzymatic metabolism by reductase and hydrosteroid dehydrogenase during hepatic first pass: high concentrations should be used to rise therapeutical effects making difficult its use in HRT. In women with non-functioning ovaries, greater bioavailability of P was determined following vaginal use than with oral administration, while blood concentration after i.m. injection was higher. However, oral and i.m. administration of P increases plasma concentration of P neuroactive metabolites such as, pregnanolone, allopregnanolone and 20-dihydroprogesterone.

The oral progestins are compounds that exhibit progestational activity and are more resistant than natural P to the first hepatic pass.

Progestins are not the same; they differ in chemical structure, structure-function relationships, metabolism, pharmacokinetic and potency. In fact, synthetic progestins can derive from testosterone (19-nortestosterone derivates such as norethisterone, levonorgestrel and gestodene), P or hydroxyprogesterone (17-OH progesterone derivates such as medroxyprogesterone acetate, clomadinoone and ciproterone acetate, and 19-norprogesterone derivates such as nestorone and nomegestrol acetate) or from spironolactone (drospirenone). Therefore, their structure can influence the affinity to PR and other steroidal receptors such as androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR) and mineralcorticoid receptor (MR); and these differences could influence their activity also in the CNS. According to their selectivity profile, these molecules will may induce divergent biological effects with respect to natural P.

The different chemical structure might induce a different metabolism; in contrast to P, not all progestins could be converted into the GABA-A receptor-active metabolite AP [1]. Some of the 19-norprogestins, in particular 19-nortestosterone-derived progestins, may have the potential to be converted to neuroactive metabolites, since they are extensively converted to 5α-, 3α-, 5α- and 3β, 5α-metabolites. Norethisterone acetate and MPA were shown to produce some anxiolytic-like effects when rats were tested in the “elevated plus maze” and the “shock-probe burying test”, supporting the concept of their metabolism into neuroactive steroids. Studies conducted in menopausal women found that the use of the estrogen alone restores the AP circulating levels, but when estrogen is associated to P or progestins, the effects on AP are different depending on the molecule it was used.

On ovariectomized (OVX) rats, different progestins (micronized progesterone (MP), medroxyprogesterone acetate (MPA), dydrogesterone (DYG), drospirenone (DRSP) and nomegestrol acetate (NOMAc)) produces different effects on the concentration of AP in specific brain areas (frontal and parietal lobe, hippocampus, hypothalamus, anterior pituitary) and in serum, while they do not seem to affect the adrenal AP concentration. The results change when the progestins are administered in association with an estrogen molecule such as estrogen valerate (E2V) (specifically, MP is active in all the brain areas analyzed and using doses of 2-4-8 mg/kg/day both administered alone and in combination with E2V. MPA augments significantly the concentration of AP in all the brain areas examined and, in combination with E2V, its action was enhanced in frontal and parietal lobes, hypothalamus and anterior pituitary. MPA does not affect neither circulating nor adrenal AP levels, suggesting that the effect observed at central levels is dependent on a direct impact of this compound on central AP content independently of a contribution from circulating levels. DYD administration reversed AP reduction after OVX in all the brain areas analyzed except the parietal lobe and the anterior pituitary. This positive influence on AP levels is also seen in the dose-dependent trend in the frontal lobe, hippocampus, and hypothalamus achieving statistical significance when DYD was administered at the highest dose (1.0 mg/kg/day) reaching levels close to those of the fertile animals. The 1.0 mg/kg/day DYD plus E2V combined therapy caused a greater increase of AP levels in the frontal lobe, hippocampus and hypothalamus compared with the effect of E2V alone. This additive aspect of DYD on estrogen-
induced effects was seen in the same brain areas when the administration of DYD alone increased AP content. It is conceivable that the strict analogy between the molecular structures of P and DYD could make this synthetic progestin a valuable substrate for the 5α-R-3α-HSD enzymatic pathways and then a substrate for the synthesis of allopregnanolone. Thus, the frontal lobe, hippocampus and hypothalamus appear to be selected brain areas targeted for DYD action in this synthesis/release of 3α, 5α-reduced metabolite of P. On the other hand, DRSP does not show any activity in the brain nor in serum on AP, evidencing a neutral impact on metabolism, even when administered with E2V.

Conversely, a positive selective influence of NOMAc on AP was shown only in the hippocampus (0.5-1.0 mg/kg/day). NOMAc combined with estrogen induced differential results depending on the diverse areas: in the hippocampus, in the hypothalamus and in the anterior pituitary the addiction of 1.0 mg/kg/day NOMAc to E2V was able to produce an even greater increase of AP levels in comparison to the effects of E2V alone. This additional feature of NOMAc was observed in those brain areas, such as hypothalamus and anterior pituitary, where the administration of NOMAc alone was not able to augment the AP content. In the serum none of the progestins used lead to an increase in AP, except MP.

This suggests that the addition of an estrogen molecule enhanced the responsiveness of selective brain areas to progestins actions on ALLO synthesis/release.

The differential interaction of synthetic progestins, respect to P, with the 5α-R-3α-HSD enzymatic system, can be hypothesized as a consequence of their different chemical structure. It has been demonstrated that progestins differentially affect 5α-R activity; for example, norgestimate blocked 5α-R activity with a IC50 value of 10 mM, followed, for inhibiting activity by levonorgestrel, dienogest, cyproterone acetate and gestodene, thus affecting the rate of AP synthesis.

References

How does oral contraception affect mood?


Nicola Pluchino
Department of Reproductive Medicine and Child Development
Section of Gynecology and Obstetrics
University of Pisa
Via Roma 35, 56100 Pisa, Italy
e-mail: nicola.pluchino@med.unipi.it