Psychological effects associated with oral contraceptives

*Violeta Trandafir, Nicoleta Cartas,
Roxana Beschea Chiriac, Loredana Catrinescu*

Violeta Trandafir – “Grigore T. Popa” University of Medicine and Pharmacy Iasi, Department of Oral and Maxillofacial Surgery

Nicoleta Cartas – Senior Psychiatrist, Socola Institute of Psychiatry Iasi

Roxana Beschea Chiriac – resident in Psychiatry, Socola Institute of Psychiatry, Iasi

Loredana Catrinescu Loredana – specialist in Psychiatry

ABSTRACT

Combined oral contraceptives (COC) are used by millions of women worldwide. Although findings are not entirely consistent, COC have been found to impact on brain function and, thus, to modulate affective processes. Even though conflicting, the data already published should make aware every prescriber that women on oral contraceptive (OC) can develop psychological problems. In this situation, physicians have to focus their attention on those cases that are at risk, like adolescents, women with depression or with previous history of hormonal contraceptive-induced adverse mood.

The current study highlights the effects of OC on fear, depression and suicidal behaviour and it is intended to be a useful tool for the medical practice of both psychiatrists and those who prescribe sexual hormones therapies.

KEYWORDS

Oral contraceptives, depression, suicide, fear

INTRODUCTION

Combined (COC) contain synthetic progesterone and estrogen analogues and are the most frequently prescribed type of hormonal contraceptives (1). They have been used widely by women of child-bearing years

since its introduction in the 1960s (10). Even then, the researchers hypothesized that large dosages of synthetic estrogens and progestins in COC (eg, 5 mg norethynodrel, 75 mg mestranol) could potentially interact with mood-related neurotransmitters and

neurotransmitter metabolism (2). In contrast to well-known physical effects, psychological and behavioural consequences of OC use have been vastly under-researched (3). Some studies show that the steroidal activity of lower-dosage modern contraceptives do not have a clinically relevant physiological impact on women's mood or mood-related neuroendocrine functioning (2). In the 2016 Medical Eligibility Criteria for Contraceptive Use report, the Centres for Disease Control and Prevention concluded there are no contraindications to hormonal contraception for women with depression, citing a lack of evidence supporting a causal relationship (4).

Nevertheless, the researchers continue to hypothesize that the use of OC might impact negatively the mental health of the women, knowing that approximately 30% of reproductive age women experience a psychiatric disorder annually (5).

STRUCTURAL CHANGES

Raymond and colleagues (2019) showed that OC users had significantly lower levels of salivary estradiol and progesterone when compared to naturally cycling women (6). This modification may be one of the causes that leads to the contraception-induced morphological changes in some brain regions. Regardless of their tissue of origin (ovaries or hippocampus), estrogens effect change by binding to estrogen receptors (ERs), which are expressed throughout the body including brain regions such as the hypothalamus, hippocampus, amygdala, cerebral cortex, basal forebrain, striatum, raphe nuclei, and cerebellum (7). A higher estradiol and/or progesterone binding after continuous OC intake might lead to a subsequent downregulation and/or to a desensitization of ER or PR. Hence, hippocampal activation could be reduced, in consequence slightly impairing learning processes (8).

This is because E2 promotes neurogenesis in the dentate gyrus, thereby providing multiple morphological substrates for encoding new memories. Physiologically, E2 rapidly facilitates excitatory synaptic transmission, decreases inhibitory synaptic transmission, and facilitates the induction of long-term potentiation. E2 also rapidly activates numerous cell-signalling cascades in the hippocampus that are essential for long-term memory formation (7).

Also the effects of estrogens on other cognitive regions of the brain have been reported, most notably in the prefrontal cortex and amygdala (7). De Bondt and his colleagues found a highly significant negative correlation of regional grey matter volume in the anterior cingulate cortex with estradiol concentrations (9). This result was only present in the natural cycle group, not in women using hormonal contraceptives. However, others studies show that the correlation between the hormonal level and this brain region is modulated by the COC. The left amygdala/anterior PHG volume decreased in women using hormonal contraceptives after three months as compared to a control group of women who did not take contraceptives (10). If COC use slows habituation in the amygdala, this could result in higher vigilance to emotional stimuli, which ultimately could lead to mood deterioration (11).

Women with a history of past COC-related mood problems showed depressive symptoms and mood swings upon re-exposure to COC in a double-blind placebo-controlled study. Their affective symptoms were paralleled by distinct activation in several emotion processing brain regions, particularly the right amygdala and the left insula (1). COC users display reduced left insula reactivity in comparison with placebo users. It has been

suggested that increased insula activation may underlie some depressive and anxious states (11).

Furthermore, COC users presented with reduced cortical thickness in the lateral orbitofrontal cortex and the posterior cingulate cortex, i.e., in regions implicated in responses to rewards and the evaluation of internal as well as external stimuli (1).

ANXIETY

OC-users detected significantly fewer facial expressions of sadness, anger and disgust, but no effects were seen on the detection of happy or fearful facial expressions (1, 12). If OC use is linked to a reduced ability to recognize emotions, this might ultimately have negative consequences for relationship quality, e.g., by leading to more conflict (3).

The observations from studies show that OC may impact women's ability to inhibit fear (13), resulting in an exaggerated and prolonged emotional response. This is because OC intake per se induced a completely changed fear learning pattern. Low estradiol levels can alter fear conditioning, even if not accessible to one's awareness, which constitutes a vulnerability factor for the development of PTSD (8). Women are more likely to experience flashback memories of a trauma if they experienced the traumatic experience in the mid-luteal phase of the menstrual cycle (14). The high progesterone levels associated with this phase, is linked with significantly greater levels of cortisol. The change in the concentration of this hormones elevates glucocorticoid receptor activation levels above the presumed threshold for memory modulation, resulting in memory enhancement of negative emotional stimuli (14).

Also, women using OC exhibit significantly poorer extinction recall compared with naturally cycling women (13) and are more susceptible to information carrying negative connotations in extremely stressful situations than under normal conditions (8).

DEPRESSION

The researchers observed that woman on therapy with sexual hormones have an increased frequency of mind wandering (6). This condition is an indirect measure of reduced attentional control and might affect one's ability to perform in daily activities. If this cognitive shortcoming overlaps a depressive disorders, it may worsen the symptomatology and delay the recovery process.

The link between OC and depression is still under researchers' attention, as long as the studies that have been published so far drew conflicting conclusions. While norethindrone containing contraception seems to have little adverse effect or even protective effect (2, 15, 16), other hormonal treatments' outcomes are still an issue of concern for the mental health.

A sub- study to a placebo-controlled randomized trial conducted by Scheuringer and colleagues (17), assessed the relationship between COC (1.5 mg estradiol and 2.5 mg norgestrolacetate) use and depression. Their conclusion was that trait anxiety levels and previous history of hormonal contraceptive-induced adverse mood are the strongest predictors for depressed mood induced by OC (17). The same results were obtained by a large cohort study in Korea (18). Also the authors observed that among women with a history of depression, OR increased linearly as the duration of OC lengthened (18).

A double-blinded, placebo-controlled randomized trial showed that women with subjective reports of previous COC-induced mood deterioration displayed depressive mood and mood swings when re-exposed to COC (ethinyl estradiol 30 mg/0.15 mg levonorgestrel) (11). These observations may be explained by the altered reactivity in the emotion circuit of the brain especially in the right amygdala and left insula, which were seen in the brain of the participants on COC.

After 12 months from contraceptive initiation, Ditch and colleagues (15) found that women aged 12- 19 years old were more likely to be diagnosed with depression (HR:1.12 (95%CI:1.05-1.19), $p < 0.001$) and less likely to be started on SSRIs.

The data acquired from the American College Health Association (ACHA) National college Health Assessment (NCHA) Surveys show that youngest women, 18–19, have a higher probability of depression associated with hormonal contraception (HC) (+4.3%) versus those not on HC therapy, and a 4.2% higher risk of academic performance issues resulting from reported depression. Among those with reported depression, the probability of academic performance issues is estimated to be 3.3% higher than those without reported depression (19).

Some longitudinal data on a large population-based sample of women in Australia show that, even though there is no association between the oral contraceptive pill (OCP) use and depressive symptoms, women who used OCP for reasons other than contraception were 1.32 (95% CI = 1.07–1.62) times as likely to report depressive symptoms as women who used OCP for contraception (20). Other researches failed to find any correlation between OC use and the risk of depressive disorders in young women (21, 22).

Compared to (naturally cycling) women, OC-users (ethinylestradiol (0.03)/levonorgestrel (0.15)) reported fewer mood-shifts between depression and elation in the mid-luteal phase of the menstrual cycle and had fewer ruminating thoughts at all phases (23).

The “International Active Surveillance Study of Women Taking Oral Contraceptives” (24) investigated the risks of short- and long- term use of an extended 24-day regimen of drospirenone and ethinylestradiol compared to 21-day regimens of drospirenone-containing combined OCs, OCs without drospirenone and levonorgestrel-containing OCs. In this prospective, controlled, noninterventional cohort study, they found similar incidence rates for severe depression (24). Also, other trial summarises that women in premenopausal period with major depressive disorder receiving combination hormone-based contraceptives showed less severe depressive symptoms, better overall physical function and a decreased number of comorbid anxiety disorders (25). This positive outcomes may be linked to beneficial effects of ethinyl estradiol, as long as they found that the participants who take progestin-only contraception may experience changes in gastrointestinal symptoms such as overeating and weight gain that influence depressive symptom profiles.

However, in a systematic review that included studies that evaluated progestin-only contraception and depression, a minority of progestin-only contraception users may experience depression symptoms, yet the most robust studies show no association between depression diagnosis and progestin-only contraception (16).

For women in the postpartum period, it seems that there is a positive association between etonogestrel use and subsequent antidepressant use and that norethindrone-only pills is protective against both subsequent depression and antidepressant use (26). The conclusion in this study was drawn after investigating 75 528 women, but it is different from other research that failed to observe the same association (27).

SUICIDE

The relationship between OC use and suicide is not clearly stated. The conclusions drawn by the researchers are conflicting. As mentioned below, there are a few prospective cohort studies that evaluated the impact of hormonal medicine upon this specific kind of violent death.

The majority of them concluded that there is no correlation between OC use and suicide. One of them is that of Colditz and colleagues (28), which present no greater risk of suicide for the OC users' comparative to the OC non-users. The Royal College of General Practitioners' oral contraception first study, after 25 years of follow-up, found no relative risk of violent death (29).

However, extending the follow-up time to 39 years for the same participants increased the risk for violent death (including suicide) in OC users, in a special way for those women who used oral contraception for longer durations (30). Even if there are some associations in this studies, they are weak with a null modification of the relative risk of death from all causes combined after adjustment.

The Nurses' Health Study' results are different from those mentioned above. They observed increased all cause mortality with longer durations of use and longer times since

last use, including an increased rate for deaths due to violence (31). Even though Charlton and colleagues found this correlation, they did not refer to suicide being specifically correlated to OC use.

Two more recent studies (Skovlund, 2018; Jung, 2019) focus especially on the association of hormonal contraception with suicide attempts and suicide. Both of them found positive correlations. The prospective Danish cohort notes that in women 15–33 years of age, hormonal contraceptive use was positively associated with a first suicide attempt, as compared with never-users (32). Adolescent women experienced the highest relative risks. The relative risk of a first suicide attempt increased rapidly after initiation of hormonal contraceptive use, compared with never use, and it remained at least doubled until 1 year after initiation.

Among 27,067 Korean women who participated in the Korea National Health and Nutrition Examination Survey (2007–2016), a total of 4,067 women (14.0%) reported they had suicide ideations or had attempted suicide, respectively. OC use was associated with an increased prevalence of suicidality (OR = 1.13, 95% CI 1.00–1.24) after adjustments for age, demographic factors, age of menarche, and lifestyle behaviours (18).

It is important to mention that the prevalence of suicidality in OC users compared to non-users is modulated by a history of depression (18). Skovlund et al, 2018, have also observed that the mediating effect of psychiatric diagnosis and antidepressant use to be approximately 30% (31).

The conflicting results from the studies mentioned might be due to different elements included in the research. One of them is of the type of the OC used by the participants, which

can lead to different approaches, due to their different impact on the brain. Also, the bottom age of the women included tends to be lower in the positive association' studies, capturing thus the entire period of hormonal exposure.

DISCUSSION

The OC are still an issue of debate in the medical word. The conflicting results seen above may be the result of the different approaches of each research. The use of estrogen, progesteron or both hormones have their own way of impacting the brain and thus the mood of the patients. Also each pill have a peculiar combination form of the main hormonal categories, which can create

difficulties when it comes to assess the outcomes of the studies in systematic reviews.

Another issue is that the trials that use validated measures of depression symptoms use a variety of scales, some of which evaluate mood or affect but do not specify depression criteria. Furthermore, the majority of the existent studies use self-assessed scales, which can be an important source of bias.

Some women stop their hormonal medication because of the depressive symptoms, and as a consequence they have to drop out of research. This might have influenced the final results of some studies. (29).

CONCLUSIONS

More awareness of possible mood implications from exogenous female sex hormones is warranted. Considering the severity of these little-recognized potential side effects of hormonal contraceptives, health professionals and women starting hormonal contraceptives should be informed about them.

Clearly, more research is necessary before additional recommendations can be firmly made. In the future, additional research with randomized control trials and validated measures would be useful to better evaluate the magnitude and causality of OC-induced psychological effects.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES

1. Armbruster D, Kirschbaum C, Strobel A: The not-so-bitter pill: Effects of combined oral contraceptives on peripheral physiological indicators of emotional reactivity. *Hormones and Behavior* 2017; 94: 96-105.
2. Stidham Hall K, Steinberg JR, Cwiak CA et al. Contraception and mental health: a commentary on the evidence and principles for practice. *American Journal of Obstetrics Gynecology*. 2015; 740-746.
3. Radkea S, Derntl B: Affective responsiveness is influenced by intake of oral contraceptives. *European Neuropsychopharmacology* 2016; 26: 1014–1019.
4. Curtis K, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *Morbidity and Mortality Weekly Report* 2016; 65(3).
5. Farr SL, Curtis KM, Robbins CL et al. Use of contraception among US women with frequent mental distress. *Contraception* 2011; 83:127-133.
6. Raymond C, Bourdona O, Cayer-Falardeau S, et al. Increased frequency of mind wandering in healthy women using oral contraceptives. *Psychoneuroendocrinology* 2019; 101:121-127.
7. Fortress AM, Frick KM. Epigenetic regulation of estrogen-dependent memory. *Frontiers in Neuroendocrinology*. 2014; 35: 530-549.
8. Merz CJ, Tabbert K, Schweckendiek J et al. Oral contraceptive usage alters the effects of cortisol on implicit fear learning. *Hormones and Behavior* 2012; 62:531–538.

9. De Bondt T, Jacquemynb Y, Van Hecke W et al. Regional gray matter volume differences and sex-hormone correlations as a function of menstrual cycle phase and hormonal contraceptives use. *Brain Research* 2013;1530: 22–31.
10. Lisofsky N, Riediger M, Gallinat J et al. Hormonal contraceptive use is associated with neural and affective changes in healthy young women. *NeuroImage* 2016; 134:597–606.
11. Gingnell M, Engman J, Frick A et al. Oral contraceptive use changes brain activity and mood in women with previous negative affect on the pill. A double-blinded, placebo-controlled randomized trial of a levonorgestrel-containing combined oral contraceptive. *Psychoneuroendocrinology* 2013; 38: 1133–1144.
12. Hamstra DA, De Rovera M, De Rijka RH et al. Oral contraceptives may alter the detection of emotions in facial expressions. *European Neuropsychopharmacology* 2014; 24: 1855–1859.
13. Graham BM, Milad MR: Blockade of Estrogen by Hormonal Contraceptives Impairs Fear Extinction in Female Rats and Women. *Biol Psychiatry*.2013; 73: 371–378.
14. Felmingham KL, Fong WC, Bryant RA et al. The impact of progesterone on memory consolidation of threatening images in women. *Psychoneuroendocrinology*.2012;37: 1896-1900.
15. Ditch S, Hansen S, Roberts T et al. Association of hormonal contraception initiation with subsequent depression diagnosis and antidepressant use in United States military health system beneficiaries: a cohort study. *Journal of Adolescent Health*. 2019; 64:23-47.
16. Worly BL, Worly BL, Gur TL et al. The relationship between progestin hormonal contraception and depression: a systematic review. *Contraception* 2018; 97:478–489.
17. Scheuringer A, Lundin C, Derntl B et al. Use of an estradiol-based combined oral contraceptives has no influence on T attentional bias or depressive symptoms in healthy women. *Psychoneuroendocrinology*. 2020; 113: 104544
18. Junga SJ, Choa SMJ, Choa HC. Association of oral contraceptive use with suicidal behavior among T representative Korean population: Results from Korea National Health and Nutrition Examination Survey (2007–2016). *Journal of Affective Disorders* 2019; 243:8–15.
19. Gregory ST, Hallb K, Quastb T et al. Hormonal Contraception, depression, and Academic Performance among T females attending college in the United States. *Psychiatry Research*. 2018; 270:111–116.
20. Dukea JM, Sibbritta DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women?. *Contraception* 2007; 75: 27–31.
21. Griksiene R, Ruksenas O: Effects of hormonal contraceptives on mental rotation and verbal fluency. *Psychoneuroendocrinology*. 2011; 36:1239-1248.
22. McKetta S, Keyes KM. Oral contraceptive use and depression among adolescents. *Annals of Epidemiology*. 2019; 29: 46e51.
23. Hamstra DA, de Kloet R, de Rovera M et al. Oral contraceptives positively affect mood in healthy PMS-free women: A longitudinal study. *Journal of Psychosomatic Research*. 2017; 103: 119–126.
24. Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives. *Contraception*. 2014; 89: 253–263.
25. Younga EA, Kornsteinb SG, Harvey AT et al. Influences of hormone-based contraception on depressive symptoms in premenopausal women with major depression. *Psychoneuroendocrinology*. 2007; 32:843–853.
26. Roberts T, Hansen S. Association of Hormonal Contraception with depression in the postpartum period. *Contraception*. 2017;96: 446–452.
27. Lawley ME, Haddada L, Burleyb K et al. Use of contraception among US women reporting postpartum depressive symptoms, pregnancy risk assessment monitoring system 2009–2011. *Contraception*. 2018; 97: 29–33.
28. Colditz GA. Oral contraceptive use and mortality during 12 years of follow-up: the nurses' health study. *Ann Intern Med*. 1994; 120:821-826.
29. Beral V, Hermon C, Kay C et al. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *British Medical Journal* January. 1999; 318.
30. Charlton B, Graham JW, Colditz A et al. Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study. *British Medical Journal* 2014; 349:6356.
31. Skovlund CW, Mørch LS, Kessing LV et al. Association of Hormonal Contraception With Suicide Attempts and Suicides. *American Journal of Psychiatry*. 2018; 175:4.

Correspondence:

Loredana Catrinescu,
Specialist in psychiatry, loredana.catrinescu@gmail.com

Submission: 24 mar 2020

Acceptance: 04 may 2020