

REVIEW

Oral Contraceptives and Depression in the Female Brain

Magali Justine de Rooy, Amsterdam University College

Abstract

It is currently not fully understood how and to what extent synthetic hormones in oral contraceptives influence the female brain and behaviour, and how this is related to the development of depression. Previous studies have resulted in different findings in this area of research; yet, the ways in which synthetic hormones in oral contraceptives influence the female body and brain are currently understudied. The aim of this paper is to shine light on the connections between endocrinology and psychological processes, while looking through a neurobiological lens. By bridging the fields of neuropsychology, neurophysiology and neuroendocrinology, this project will start to sketch a holistic overview of the effects of synthetic hormones in oral contraceptives, in relation to high depression rates in females. By analyzing the effects of synthetic hormones on brain structure and function, we learn more about their connection to depression; more knowledge on this subject could ultimately be used to improve psychological well being in females.

Introduction

Around the world, around 100,000,000 women use the oral contraception pill, which makes it the most used contraceptive method worldwide. These contraceptives often have side effects that include mood disorders, in particular depression. According to the oral contraception pill's instructions, depression or depressive symptoms occur in 'up to 1 in every 10 women' [1]. Depressive mood is one of the main reasons for discontinuation of oral contraceptive use [2], yet the neurological and psychological effects of synthetic hormones in oral contraceptives have barely been studied [3]. This fact raises the question of how exactly oral contraceptives influence the female brain, and how this is related to depression.

Previous studies investigating the depressive effects of synthetic hormones have illustrated a number of neurophysiological and neuropsychological results, related to depressive mood. Findings have shown that females that use oral contraceptives have higher rates of depression, among other mental disturbances, than non-users [2, 4]. Different oral contraceptives contain different types of estradiol and progestins, and these consequently influence the body and brain in different manners [3, 5]. Studies have shown that the estradiol and progestin in oral contraceptives strongly influence bodily homeosta-

sis, and therefore may alter the levels of endogenous hormones and neurotransmitters related to depression [3]. The use of oral contraceptives can also induce structural changes in the brain [6]; it is important to study and evaluate these changes, and analyze their effects on brain function and ultimately, psychological well-being.

Using and analyzing previous research, this paper will start to sketch a comprehensive and holistic overview of the effects of synthetic hormones in oral contraceptives, in relation to high depression rates in females. Taking into account that there are different levels of vulnerability towards developing mood disorders, it is important to focus on individual risk factors related to oral contraceptive use, in order to assess and ultimately prevent adverse mood effects [7]. Ultimately, this project aims at unraveling the way oral contraceptives influence the female brain, and how this is related to depression; it does this by bridging the fields of neuropsychology, neurophysiology and neuroendocrinology.

Hormonal components of oral contraceptives

It is first of all important to acknowledge that there are significant differences between, on one hand the endogenous estrogen and progesterone, and on the other hand the estradiols and progestins in oral con-

traceptives [3]. This explains why oral contraceptive pills are able to induce physical and psychological changes that are not necessarily induced by natural levels of endogenous hormones [3]. Previous research has already shown that different types of oral contraceptives influence physiology and psychology in different manners [3]. Pharmaceutical companies produce many different types of oral contraceptive pills, each with their own composition of synthetic hormones. A commonly prescribed type of combined oral contraceptive pill contains “0.02-0.04mg ethinylestradiol (EE) and varying levels of progestins” [3]. A study by Sitruk-Ware & Nath mentions characteristics of the different estrogens that are most often used in oral contraceptives: while the synthetic estrogen Ethinyl-Estradiol (EE) is more potent, it has more negative physiological side effects when compared to natural estrogens such as 17β -estradiol (E2), Estrone (E1), Estradiol valerate (E2V) and Estetrol (E4) [5]. In combined oral contraceptive pills, the estrogenic effects of the estradiol are modulated by progestin. There are different generations progestins: while older generation progestins such as Levonorgestrel and Desogestrel exert androgenic actions and may promote masculinization, newer generation progestins such as Dienogest and Drospirenone exert anti-androgenic actions and may promote feminization of the brain [3, 5].

Etiology of depression

Worldwide, an estimated 350 million people suffer from depression, and women are affected twice as often, when compared to men [8]. According to the DSM-V handbook, Major Depressive Disorder can be diagnosed by one of two symptoms: ‘depressed or irritable mood’ or ‘decreased interest in pleasurable activities and ability to experience pleasure’, combined with a number of other symptoms regarding mood and behaviour, such as ‘insomnia of hypersomnia’, ‘significant weight gain or loss’, or ‘fatigue or loss of energy’ [9]. While these diagnostic criteria give an indication of an individual’s mental health, clinical and sub-clinical depression is often also viewed on a spectrum, with varying influences on the person’s mood and affect: mood being described as “a more pervasive and sustained emotional ‘climate’” while affect is described as “more fluctuating changes in emotional ‘weather’” [2, 9]. Older models of depression suggest that

there is a single compound or brain structure responsible for the development of the disease; an often-mentioned neurotransmitter related to depression is serotonin [10]. While it is clear that amines like serotonin and dopamine play a role in depressive disorders, these mono-amine hypotheses have been disregarded as more became clear about brain structure and function. New paradigms therefore suggest that depressive symptoms are increasingly linked to malfunctioning brain circuits, and that depression develops during an interaction between amines, neuro-anatomy, neuro-connectivity, and might even have connections to hormonal axes [11]. While depression is usually seen as an idiopathic disease or as a response to stressful periods or negative life events, studies in various diseases have shown that depression or depressive symptoms can be secondary to underlying neuroanatomical changes, or might even have an exogenous cause [12]. Due to the fact that the etiology of depression is not yet fully understood, it currently is difficult to assess whether depressive symptoms are part of a depressive disorder, and what may be their underlying cause. Regarding previous knowledge, important research questions arise regarding the well-known adverse mood effects of oral contraceptives, and their relation to depression.

Psychological effects of oral contraceptives

Sparked by numerous psychological associations with oral contraceptives, research has concluded that females that use oral contraceptives have higher rates of clinical and subclinical depression, among other mental disturbances, than non-users [2, 4] When compared to a group of diaphragm users, oral contraceptive users had four times as many suicide attempts in a study by Robinson et al. [4]. Alongside depression, oral contraceptive use has been related to negative mood and affect alterations [2]. A key player that is influenced by estradiol is serotonin; while enhanced serotonin levels often lead to mood improvement, decreased serotonin levels are related to depressive mood [10]. Elevated estradiol levels are found to enhance mood, due to their serotonin-enhancing actions. It was also found that during usage of oral contraceptives, endogenous estrogen levels decline, as estrogen is replaced with a synthetic version [3]. When the serotonin-enhancing estrogen levels decline, a natural consequence is that serotonin levels also decline. A

decrease in serotonin levels has been shown to relate to depression [10]; this suggests that because the intake of oral contraceptives leads to decline of serotonin levels, it might relate to an increased susceptibility to depression. Findings on progestins are ambiguous: the effect on endogenous progesterone levels is similar to that of estrogen levels, however, low concentrations of progesterone in certain studies have found to improve mood [3]. On the contrary, other research has shown that progesterone-withdrawal can induce depressive symptoms and behaviour in rodents, suggesting that low levels of progesterone might increase vulnerability to negative mood changes [13]. Another suggestion from literature is that females who develop mood disorders during oral contraceptive use are generally more vulnerable towards developing mood disorders, regardless of their contraceptive method [14]. It is therefore important to focus on individual risk factors related to oral contraceptive use, in order to assess and ultimately prevent adverse mood effects [7].

Neurobiological structural effects of oral contraceptives

It is then helpful to assemble and review neurobiological, structural, and functional brain differences between oral contraceptive users and non-users. Recent studies have found that there are certain brain structures that are enlarged in oral contraceptive users when compared to both non-using females and males. Research by Pletzer et al. [6] has shown that the pre- and post-central gyri, parahippocampal and fusiform gyri, prefrontal cortex and temporal regions are significantly enlarged in oral contraceptive users, compared to non-using females. The parahippocampal and fusiform gyri are larger in males than in females, indicating that during oral contraceptive use in females, these regions approach the size of the male structures [6]. More current research by Pletzer and Kerschbaum [3] confirmed that oral contraceptives might masculinize brain structure, function and behaviour. It is proposed that this is the case either because testosterone levels increase, due to lower progesterone levels induced by higher progestin levels, or because estrogen levels increase, due to aromatase converting this testosterone to estrogen [3]. Simultaneously, in the earlier study by Pletzer et al. [6], the prefrontal cortex and pre- and postcentral gyri are already larger in females than

in males, indicating that oral contraceptive use increases the size difference between females and males. Research by de Bondt et al. [15] found that gray matter volumes in the anterior cingulate cortex are significantly larger in oral contraceptive users compared to non-users. This area is usually already larger in females than males, and associated with emotional memory processing (citation emotional memory processing). Two explanations for the found structural enlargements, proposed by Pletzer and Kerschbaum are that either estrogen receptors mediate and increase synaptic spine density, or that astrocyte volume increases in response to estradiol levels [3].

Neurobiological functional effects of oral contraceptives

A study by Mordecai et al. found that oral contraceptive users showed enhanced verbal memory skills compared to non-users. These enhanced skills are more pronounced during their active pill phase when compared to the inactive pill phase. Findings from this research are in line with previous findings, which suggested that suppressed or absent ovarian hormone levels lead to a decline in verbal memory skills [16]. Furthermore, it has been shown that hormonal oral contraceptive use can lead to improved dream recall compared to non-users [3]; surprisingly enough, depressed individuals usually score lower on dream recall tests when compared to healthy individuals [17]. Furthermore, research by Wharton et al. showed findings that relate to performance on spatial memory tasks: oral contraceptive users were better at mental rotation tasks when compared to non-users [18]. Interestingly enough, performance at spatial memory tasks did not only correlate with oral contraceptive use, but also with the type of progestin in the Pill. Pills containing an anti-androgenic progestin performed worse on the task than non-users. Because men usually perform better than women at this task, these results are in agreement with the finding that anti-androgenic progestins may exert feminizing effects on the brain [3].

Conclusion

Important findings regarding the effects and side effects of oral contraceptive use and its relation to depression are scattered among different studies and in multiple disciplines. It has been shown that estra-

diol and progestin in oral contraceptives can alter mood and even induce subclinical or clinical depression, by altering brain structure and function in various ways. Current research is investigating these effects more closely, however, theoretical findings are not yet being directly transferred into practice with regards to oral contraceptive prescription. A limitation of oral contraceptive research arises, due to the fact that the complete etiology of depression is not yet fully understood. It is extremely difficult to assess what clinical or subclinical depressive symptoms might be caused by oral contraceptive use, when the mechanisms by which Major Depression Disorder develops are still not completely clear. There is a need for further research in women who discontinued their oral contraceptive use: many existing studies focus on satisfied oral contraceptive users, while undesirable side effects such as negative mood changes and depression will likely be most prevalent in women who have discontinued their Pill use. Most urgently, within-subject studies are needed in a group of women who compare their physiological and psychological state before, during and after a period of oral contraceptive use, in order to unravel the exact connections between hormonal oral contraceptives and depression.

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