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Oral contraceptives and affective disorders: neurobiology and informed choice

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Oral contraceptives and affective disorders: neurobiology and informed choice

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Contents

Abstract

Pregnancy prevention and female reproductive freedom have been some of the most contested political issues for decades. Abortion, a fundamental part of women's healthcare, divides liberals and conservatives on an international scale. The consequences of unintended pregnancy without safe and reliable contraception are widespread, disproportionately impacting women of color, trans and non-binary folks, and poorer communities. The birth control pill is the most common form of oral contraception (OC) globally. Many people with ovaries begin the pill or other hormonal contraceptive (HC) methods as young as 11 years old. Exogenous progesterone and estrogen are known to impact mood, affect, physiology, and behavior. Ongoing research examining the relationship between OCs and affective disorders has yielded controversial results. Studies in various countries have different conclusions – a significant negative correlation with OC use and positive affect, some significant negative effect depending on age, or no significant relationship with mental health or quality of life between women taking or not taking OCs. Young women are more likely to develop an affective disorder like depression than men of the same age group. This vulnerability cannot be overlooked when considering the effects of HCs on mood. This review analyzes and contextualizes current data on the relationship between OCs and mental health disorders and provides future directions for research on this topic.

Introduction

"My body, my choice." "Reproductive rights are human rights." "Bans off our bodies." These are phrases chanted by crowds, written on shirts and poster boards, and broadcasted in newsrooms around the globe. Powerful slogans such as these have arisen from the attack on emergency contraception as women have and will continue to suffer the consequences of unintended pregnancy. Contraception, abortion, and reproductive rights have been an issue at the forefront of social justice and equitable healthcare access movements for decades. Losing reproductive rights for those with uteruses has devastating consequences, especially affecting non-white, transgender, nonbinary, and poorer citizens. Now more than ever, discussions surrounding hormones and society are crucial to improving care for vulnerable groups. One common side effect of hormonal birth control is a change in mood, and the negative mental health effects associated with hormonal contraception are vital to consider when choosing a contraceptive method. A push for increased awareness and informed choice is needed.

Reproductive choice is a vital source of autonomy for people with ovaries. With the overturning of *Roe v. Wade* by the United States Supreme Court in June 2022, access to abortion is not a national protection for the first time since 1973. This decision, made by a majority conservative court of justices, caused an eruption of outrage across the United States and internationally. There were many people not protected by *Roe* before, and now the impact of its overturning is more widespread. The federal abortion ban has already taken hold in many states. For example, Idaho is now enforcing its trigger ban which criminalizes abortion and emergency contraception (*Birth Control*, 2022a). On September 23, 2022, the General Counsel at the University of Idaho sent an email to all University of Idaho employees prohibiting them from

> "taking any action, and from using or providing institution funds or facilities, for any of the following: Promoting abortion; Providing or performing an abortion; Counseling in favor of abortion; Referring for abortion; Providing facilities for an abortion or for training to provide or perform an abortion; Dispensing drugs classified as emergency contraception by the FDA, except in the case of rape as defined in section 18- 6101, Idaho Code; Contracting with abortion providers; and Advertising or promoting services for abortion or for the prevention of conception" (*University of Idaho Guidance on Abortion Laws - DocumentCloud*, n.d.).

In response to this new ruling, Rebecca Gibron, the regional CEO of Planned Parenthood that provides services in Idaho, stated "These attacks on birth control are not theoretical. They are already happening…The University of Idaho's new policy is just the latest example of extremists and draconian laws threatening to strip us of all control over their reproductive health care" (Boone, 2022). This is just one example of an institutional response to the battle over abortion rights. There are a multitude more of attacks on reproductive freedom in other states.

The disruption pregnancy can cause to education, careers, and entire lifestyles is not trivial, in addition to the known negative health outcomes and adverse economic effects of unintended pregnancy. Lack of access to contraception and reproductive healthcare puts people with uteruses at risk the most for mental and emotional distress in the general population. In the United States, almost half of all pregnancies are unintended (Skracic et al., 2021). Pregnancies may need to be terminated for medical reasons to preserve the health of the mother or to abort a fetus that has low or no chance of survival. Access to contraception and safe abortion is essential to maintaining the wellbeing of women in America and all over the world. Local, national, and global action to improve sexual safety, pregnancy, and reproductive healthcare is necessary to

give equal footing to people of all genders so they can take care of their bodies and afford more choice in their life.

Hormonal birth control is the most widespread method of hormone treatment among the general population, with more than 100 million women worldwide using OCs (Christin-Maitre, 2013). According to United Nations data in 2009, 62.7% of women globally of reproductive age who were married or in unions used COCs, although there are major disparities internationally in universal reproductive health (Christin-Maitre, 2013). A contraceptive is defined as a service, surgery, or medicine designed to prevent pregnancy (*Birth Control*, 2022). National data from the CDC reports that during 2017-2019, 65.3% of women aged 15-49 in the United States were using contraception, and approximately 14.0% of this group was on the pill (Daniels, 2020). Given the prevalence of this hormonal treatment and the ongoing mental health epidemic, it is vital that the relationship between HCs and mental health issues like depression is analyzed. Other popular methods of hormonal contraception include intrauterine devices (IUDs) and implants like Nexplanon, but I will be solely focusing on the research pertaining to OCs, as they are the oldest and most widely used method of hormonal birth control. OCs or combined oral contraceptives (COCs) are widely accessible, offered through prescriptions and available in some community and school health centers. The broad accessibility to this birth control method and ease of taking it orally is one of the reasons it is so popular.

Teenage and young adult populations are currently experiencing a mental health crisis, and birth control could play a role. 16% of youth aged 12-17 in America have suffered from at least one depressive episode in the past year and report that their depression severely impairs their ability to function in their daily life. 59.8% of this group do not receive any mental health treatment (*The State of Mental Health in America*, n.d.). Likely factors in the development of this

disorder include social isolation associated with the global COVID-19 pandemic, familial, social, and academic pressures (Geiger & Davis, 2019). Mental health disorders including major depressive disorder (MDD) and generalized anxiety disorder (GAD) are some of the leading causes of disability worldwide. Notably, women are 70% more likely to experience a depressive disorder and 60% more likely to experience an anxiety disorder than men (Hall et al., 2015). This elevated risk contributes to higher rates of unintended pregnancy among women with these mental health issues.

The relation between OCs and mental health issues is controversial and there are conflicting results from well-known, international studies. For some people, taking OCs may have a stabilizing effect on pre-existing depressive mood, but for others there can be a tendency for their affect to worsen (Duke et al., 2007). Generally, the highest risk group is women with a history of affective disorders or premenstrual dysphoric syndrome (Fruzzetti & Fidecicchi, 2020). Data from a large study done in Australia shows that within the general population, the overall association between depressive symptoms and OC use is not statistically significant, but people who take OCs for non-contraceptive reasons report an increase in depressive symptoms (Duke et al., 2007). A different study in Denmark found that use of HCs was associated with subsequent diagnosis and treatment for depression (Robakis et al., 2019). This area can be particularly difficult to study and to control for confounding factors since depressive symptoms and negative affect can present in various ways. Regardless, the prevalence of mental health issues is too great right now to ignore the evidence.

Understanding the effects of hormones on the body can have broader impacts, including improvements in gender-affirming hormone therapy (GAHT). This review of OCs and their relation to mental health issues will present the current findings and suggest further directions for

research. The history of global birth control is well-studied, and I will be selective in that which pertains directly to recent research in the relationship between OCs and depression.

Affective Disorders

Affective disorders are one of the largest global disabilities. Depression, also diagnosed as major depressive disorder (MDD) or clinical depression, is a common mood disorder with psychological, emotional, and behavioral impacts. In the United States, approximately 18 million individuals, or one in ten people, experience depression every year (Kessler et al., 2005). Depression is an extremely paralyzing and exhausting illness and disproportionately affects women (Seney et al., 2022). Adolescents are also particularly at risk. In the United States alone, 16.39% of young adults 12-17 years old (almost 2 out of every 10 teens) reported suffering from at least one major depressive episode in the past year, and 60% of teenagers with MDD do not receive proper mental health treatment (*The State of Mental Health in America*, n.d.). There are many factors contributing to this recent spike in depressive diagnosis, including but not limited to the global pandemic, capitalistic pressure, a polarized political culture, climate change, and struggles with gender and sexual identity. Since women are known to be at a higher risk of developing an affective disorder, understanding the impact of hormonal birth control on brain and behavior is imperative at this time.

Adolescents, women, and minority groups are particularly at risk of experiencing depression due to social and occupational pressures and societal issues like racism, sexism, homophobia, and transphobia. The 2017 National Survey on Drug Use and Health in the United States reported that mental illness is more prevalent among women (22.3%) than men (15.1%), with young women aged 18-25 years old at the most risk (McCloskey et al., 2021). This sex difference in depression

has many contributing external and biological factors. Women generally have more severe symptoms, more subjective distress, and are more likely to seek treatment (Seney et al., 2022). Studying the influence of OCs on the occurrence of depressive symptoms is important to understand the multifactorial mental health effects of the pill and to provide more guidance to women experiencing depression so they can make informed choices about their birth control method.

Symptoms of depression can range in severity and often cause issues in academic, occupational, athletic, familial, or other social settings. Depression is also closely associated with other mental health disorders such as anxiety and bipolar I and II. This mood disorder can be triggered by a traumatic event or develop during a critical period like adolescence (McKetta & Keyes, 2019). Some people are more at risk due to a family history, health risks, or socioeconomic circumstances. Pharmaceutical drug treatment and comorbid disorders vary based on gender, but once MDD has been diagnosed, the prognosis is similar in women and men. To be clinically diagnosed with depression, a patient must exhibit at least five of the following symptoms (as listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM)) over a period of at least two weeks:

1. Depressed mood (apathy, sadness) most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (lack of motivation).
3. Significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day.
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5. Fatigue or loss of energy nearly every day.

6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8. Recurrent thoughts of death, recurring suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. (Truschel, 2022).

There are various treatment options for depression. An estimated 40-50% of women of reproductive age receive prescription pharmacotherapy to treat depression and anxiety (Berry-Bibee et al., 2016). There are many classifications of antidepressants that act differently on the brain and have differing efficacy based on individual variation in brain chemistry. These include selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (*Overview - Antidepressants*, 2021). Many of these medications target the reuptake of neurotransmitters serotonin and dopamine in the synapse of neurons because of their close associations with mood. Psychotherapy or clinical counseling is often coupled with pharmacological treatment to increase positive outcomes.

Types of Contraceptives

Consistent and safe use of contraceptives in the United States varies based on age, education, location, and access to affordable healthcare. Successful pregnancy prevention can be achieved though barriers, hormonal methods, long-acting reversible contraceptives (LARCs), sterilization, or other fertility-based awareness methods (*Birth Control*, 2022). Some types of birth control are reversible, whereas others may be permanent. Although pregnancy prevention is a common reason many people choose to start birth control, other desired outcomes, such as

reduced menstrual bleeding, may be a reason that contraceptives are prescribed. Table 1 outlines the main types of birth control methods and their primary mechanisms.

Type	Mechanism	Example(s)
Barriers *71-85% effective*	Prevent sperm from entering the cervix or uterus	• Male condoms • Female condoms • Contraceptive sponges • Spermicides • Diaphragms/cervical caps
Hormonal contraceptives (HCs) *99% effective*	Impact the endocrine system and the regulation of hormones in a person's body by introducing exogenous hormones	• Oral contraceptives (the pill) • Contraceptive patches • Vaginal rings • Injectable birth control • Arm implants (Nexplanon)
Long-acting reversible contraceptives (LARCs) *99% effective*	Placed in the uterus via a medical procedure, can last 3-10 years, depending on the specific type	• Intrauterine devices (IUDs)
Sterilization *99% effective*	Permanent route to preventing pregnancy (surgical)	• Tubal ligation • Vasectomy
Fertility-based awareness methods *77-98% effective*	Timing and placement there is no sperm present when an egg is present	• Menstrual cycle tracking • Withdrawal

Table 1. Birth control methods, including efficacy ("Birth Control," 2022.).

The first hormonal pill was approved by the FDA in 1960 and contained extremely high doses of estrogen. This made it 100% effective, but induced moderate to severe side effects such as headaches, nausea, sore breasts, and changes in menstruation (early or late periods, spotting, or no bleeding) (*What Are the Side Effects of the Birth Control Pill?*). Over time, the pill has undergone changes in its chemical composition to lower the dose of estrogen and include progestins to improve tolerance, reduce side effects, and better mimic the natural human menstrual cycle (Christin-Maitre, 2013). There are two types of OCs; monophasic pills provide the same level of hormones throughout the three weeks, whereas triphasic pills give three different amounts of hormones over the three weeks to closer mimic the body's physiology (Van

Vliet et al., 2011). COCs used to be used as a form of emergency contraception (used to prevent pregnancy after sexual intercourse without a barrier or other form of birth control), but due to the frequent and severe side effects like nausea, vomiting, headaches, and spotting, a progestin-only type of emergency contraception is now used.

Mechanism of Action of Oral Contraceptives

All types of hormone therapy, including birth control, can change an individual's neurobiology and endocrine make-up. The endocrine system is a chemical messenger network that uses the bloodstream to transport hormones to target tissues all over the body. The impact of neuroendocrinology is often underemphasized even though the influence of hormones is widespread. Varying concentrations of hormones in the blood and the number of receptors can cause individual behavioral differences.

The primary mechanism of OCs is prevention of ovulation during the menstrual cycle. The menstrual cycle serves the purpose of preparing the body for reproduction. Broadly, menstruation can be broken into two phases: preparation for conception, which is coordinated by estrogen, and preparation for implantation and maintenance of the pregnancy, if it occurs, which is coordinated by progesterone (Hill, 2019). Preparation for conception is referred to as the follicular phase and begins on day 1 when period bleeding starts and ends around day 10-14 when a mature egg is released from an ovary (ovulation). Estrogen is dominant during this stage and steadily increases over the first 14 days, peaking just before ovulation. Preparation for implantation is called the luteal phase and begins after ovulation. During this phase, a temporary endocrine structure, the corpus luteum, forms from the follicle following ovulation of the mature

oocyte and produces progesterone (Hill, 2019). Progesterone steadily increases across the second phase of the menstrual cycle and generally peaks between days 20-22 (see Figure 1).

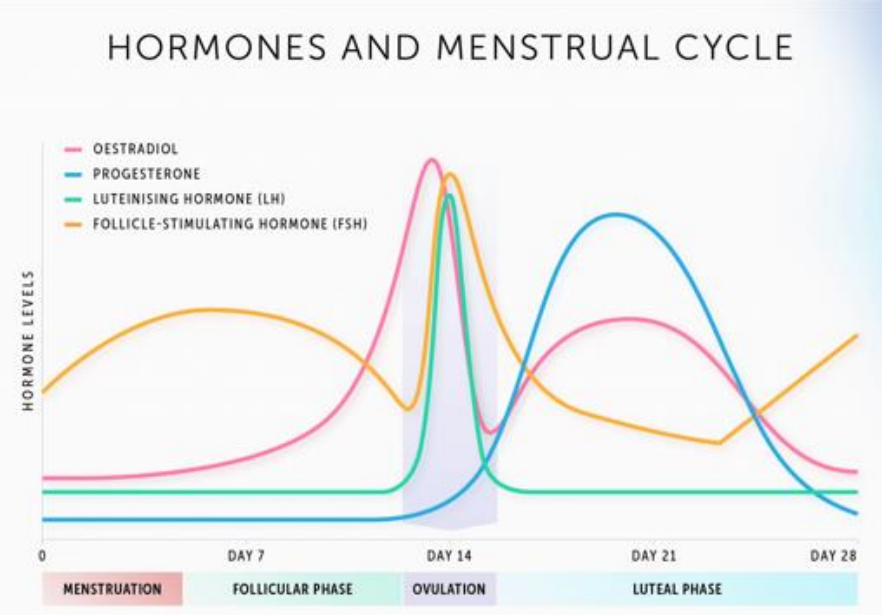


Figure 1. Hormonal changes during the phases of a natural menstrual cycle (*Menstrual Cycle*, 2021).

Behavior and mood can fluctuate during each phase due to the hormonal changes occurring in the body. Studies have shown that sexual desire increases during the periovulatory phase, which is the five days prior to ovulation and during the 24 hours of ovulation (Hill, 2019). This change in social behavior can be attributed to the evolutionary need to reproduce, since selection has resulted in higher expression of reproductive behaviors at the time when pregnancy is possible. For pregnancy to occur, sperm needs to enter the uterus to be in close enough proximity of the mature egg, and thus there is an increase in sexual desire during this time. These changes are driven by the increase in estrogen during the follicular phase. HCs like the pill target this estrogen surge that leads to ovulation, so sexual side effects can occur.

The menstrual cycle is coordinated through the hypothalamic-pituitary-gonadal (HPG) axis. This pathway includes the hypothalamus, the anterior pituitary gland, and ovaries (Hill,

2019). Gonadotropin-releasing hormone (GnRH) is released from the preoptic area of the hypothalamus, and in response to GnRH, the anterior pituitary gland releases follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which travel through the bloodstream to the ovaries. FSH and LH stimulate the ovaries to begin maturation of follicles, causing estrogen to be secreted. Next, the mature egg is released during ovulation and if it is not fertilized, the corpus luteum forms from the ruptured egg follicle and produces progesterone. The corpus luteum persists if there is pregnancy and continues to produce progesterone, and degenerates if there is no pregnancy. The HPG axis is regulated using multiple feedback loops. When the brain and pituitary gland detect that estrogen and progesterone levels are low because the body is not pregnant, initiation of hormone release begins again so that follicle development can occur. Simultaneously high estrogen and low progesterone levels are indicative of egg maturation, and the brain sends a signal to secrete LH, promoting ovulation (Hill, 2019). When estrogen and progesterone are both in high concentration after ovulation, the brain and pituitary are signaled to decrease hormone release so that fertilization and implantation can occur.

Development of this method of birth control was based on previous knowledge that progesterone is responsible for suppressing ovulation during pregnancy (Rivera et al., 1999). Initially, these COCs were called anovulatories and used synthetic progestins. Their effect on ovarian function is three-fold: they inhibit follicular development, ovulation, and corpus luteum formation. The role of the corpus luteum is to make the uterus a healthy environment for a fetus to develop. To do this, the corpus luteum secretes progesterone, which thickens the endometrial lining so an egg can implant there and keeps a steady supply of oxygen and blood flowing to that region in case the egg is fertilized and a fetus begins to develop (*Corpus Luteum*, n.d.). The ovarian effects of COCs occur because of the inhibition of pituitary production and secretion of

FSH and LH. In other words, the pill mimics the portion of the cycle where FSH and LH are at a stable level and secretion of these hormones can decrease. When ovarian hormones are maintained at a sufficiently high level, the hypothalamus receives positive feedback and sends a signal to the pituitary to reduce the secretion of gonadotropins, so ovulation does not occur and pregnancy cannot happen (Rivera et al., 1999). OCs and COCs provide a consistent daily dose of estrogen and progestin, which is a synthetic progesterone (Hill, 2019). Over time, this dosage has developed to be analogous to the progesterone-dominant phase of the menstrual cycle (see Figure 2).

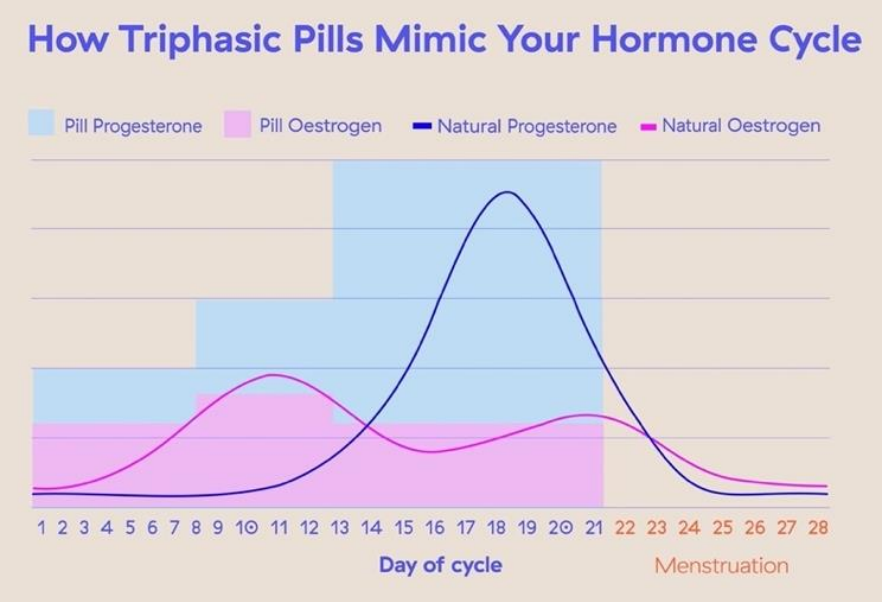


Figure 2. Exogenous hormones from a triphasic OC and control of estrogen and progesterone over the course of a single menstrual cycle (Kin, 2022).

Mental Health Effects of Oral Contraceptives

The relationship between birth control use, mental health disorders, and quality of life has been well-studied. HCs like the pill, patches, and IUDs alter the endocrine system, which in turn

can cause changes in brain and behavior that can vary across individuals. There is contrasting evidence to support significant or non-significant negative mental health effects of the pill.

One of the reasons women are at twice the risk of depressive disorders than men may be exogenous hormone use like oral contraception (McKetta & Keyes, 2019). During periods of estrogen instability like the peak and successive sharp decline of estradiol during ovulation, mood changes that interfere with daily function are more likely to occur. Importantly, the onset of depression is linked to times when estrogen levels are low in comparison to progesterone levels (Rybaczyk et al., 2005). Some OCs are prescribed to try to mediate these symptoms with a daily dose of estrogen and progesterone. However, exogenous hormone use can increase the likelihood of an affective disorder like depression and cause changes in mood (McKetta & Keyes, 2019).

Mental and emotional side effects of OCs include increased depression, anxiety, anger, compulsion, and changes in attraction, arousal, and sexual desire. In humans, exogenous sex-hormones can influence gene expression in emotion-regulating areas of the brain like the amygdala, prefrontal cortex, and hippocampus (de Wit et al., 2020). Teenagers are especially vulnerable to neurobiological changes because their brains are still maturing; in particular, the prefrontal cortex is not fully connected to the amygdala yet, so neural networks regulating emotion and cognition are still forming.

Other than teens, a vulnerable group to call attention to is women with psychiatric disorders, who are more likely to experience unintended pregnancies due to inconsistent use or non-use of contraceptives (McCloskey et al., 2021). New episodes of a psychiatric disorder can be coupled with an unintended pregnancy due to cognitive impairment, a decreased capacity for risk-assessment, and inconsistent contraceptive use. Additionally, there are health risks of

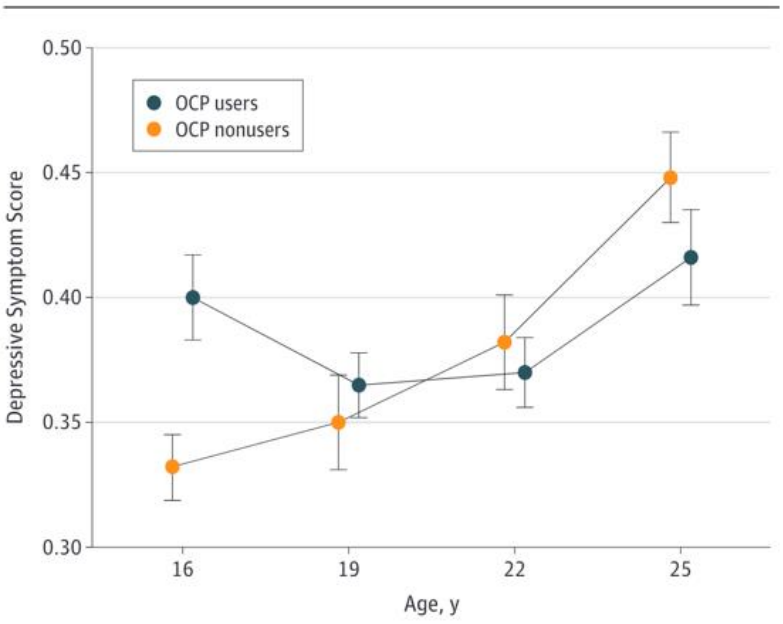
pregnancy for women with a mental illness due to the changes in hormones that may compromise efficacy of psychotropic medications (McCloskey et al., 2021).

Fluctuations in sex-hormones estrogen and progesterone can cause mood changes and put women at a higher risk for depression (Slavich & Sacher, 2019). Immune cells have sex-hormone receptors, so high and low concentrations of ovarian hormones have direct anti-inflammatory or proinflammatory effects, respectively. These changes can increase the individual likelihood of developing MDD over time (Slavich & Sacher, 2019). In addition, sex-hormones impact the activity of serotonin and dopamine. These neurotransmitters heavily influence mood stability and may be affected in some people with mental health disorders. There is some evidence that estrogen can be neuroprotective in certain regions of the brain and facilitate serotonergic transmission (Shors, 2003). A recent study showed that estrogen can protect the hypothalamus, hippocampus, amygdala and brainstem from neurodegenerative disease, cognitive decline and affective disorders (Mu & Kulkarni, 2022). Incidences of post-partum depression (PPD), a mood disorder occurring in the weeks or months following birth, are strong evidence for the role of estrogen in affect. PPD occurs in 6.5-20% of women, and it has social, hormonal and genetic risk factors (Mughal et al., 2022). The neuroendocrine pathophysiology of PPD points to the fluctuation of estrogen and other reproductive hormones during and after pregnancy as the cause of this mood disorder. Treatment for PPD often includes antidepressant medications that target serotonin receptors. This is an effective pharmacotherapy due to direct serotonin-estrogen interactions (Rybaczyk et al., 2005). It could be inferred from this research that changes in estrogen and progesterone levels because of OCs can influence mood.

Unlike estrogen, progesterone can worsen mood due to inhibition of glutamate transmission (Mu & Kulkarni, 2022). The mechanism behind this phenomenon is complex. Glutamate blood levels are inversely related to progesterone and estrogen levels (Zlotnik et al., 2011). As the main excitatory neurotransmitter in your brain, alterations to concentrations of glutamate can have a direct impact on neuronal connections. The presence of progesterone can increase amounts of monoamine oxidase, an enzyme which removes serotonin and dopamine from the brain. Increased concentrations of this enzyme would reduce serotonin concentrations in the synapse, possibly leading to worsened mood or severe changes in affect (Mu & Kulkarni, 2022). Given the neuroprotective but potentially damaging mood effects of estrogen and progesterone, exogenous introduction of these hormones to the body through the pill could cause a decrease in mental health and well-being.

There is increasing evidence that OCs can cause an increase in negative mood symptoms. A large review of 13 studies was published in 2002 that revealed differences in affect between OC users and non-OC users (Mu & Kulkarni, 2022). Some forms of hormonal contraception can perpetuate depressive symptoms in individual users. This relationship and the likelihood of the development or increased severity of a mood disorder depends on the amount and type of progesterone contained in the pill. In a recent study, women taking a monophasic preparation of an OC that contained estradiol reported more positive mood symptoms than other OCs they had previously taken (Mu & Kulkarni, 2022). They concluded that progesterone-only contraception can be associated with increased depression, and suggested medical providers use caution when prescribing this type of contraception to women with a history of depression or those that are experiencing current mental health issues.

Additionally, in a 2006-2015 Dutch study, TRAILS (Tracking Adolescent's Individual Lives Survey) data from young women from 13-25 years old was used to analyze the prevalence of OC use and depression. Their conclusions varied based on age group; 16-year-old women using OCs did report higher concurrent depressive symptoms than those in the same age group that did not use OCs (de Wit et al., 2020) (see Figure 3). Based on these findings, it is important to understand and monitor negative mood symptoms in OC users in vulnerable age groups like teenagers (de Wit et al., 2020).



Data are (adjusted) mean values with 1 SE for the depressive symptom score through multilevel analysis (ie, mixed models). Analyses were adjusted for age, ethnicity, and socioeconomic status (β coefficient for interaction = −0.021 [95% CI, −0.038 to −0.005; *P* = .0096]).

Figure 3. OC use and depressive symptom scores across age groups of recent study in the Netherlands, showing significantly increased depressive symptoms in OCP (OC) users around the age of 16 (de Wit et al., 2020).

A national study in the United States (McKetta & Keyes, 2019) did not find an association between OC use and current or lifetime depressive disorders. This research team used

data from the National Comorbidity Survey-Adolescent Supplement (NCS-A), which included self-reports of timing and duration of OCP (OC) use as well as timing of depressive episode onset in people aged 13-18 (McKetta & Keyes, 2019). In the 4,765 female respondents, 671 (14%) reported ever using OCs and 405 (60%) of this group were current users. 871 women (18%) met criteria for lifetime depression (meaning they had a diagnosis of major depression, minor depression, or irritable major or minor depression), and 202 (23%) of them were currently experiencing depression (McKetta & Keyes, 2019). From this survey, they concluded that there was no link between OC use the development of depression.

A similar survey conducted in Australia (Duke et al., 2007) also addressed the use of OCs and depression in young women and found the same result: an insignificant independent effect of OC use on depression (see Figure 4). They used data from the "young cohort" (18-23 years old) of the Australian Longitudinal Study on Women's Health (ALSWH), a large population-based longitudinal study of women in which both OC use and the experience of depressive symptoms was measured over time. In total, they analyzed data from two different "Survey" groups – distinguished by year of data collection. Survey 2 included 8636 women and was conducted in 2000 and Survey 3 included 7489 women and was conducted in 2003. On Survey 3, 23.3% of OC users and 30.3% of non-OC users reported depressive symptoms. Non-OC users had a 1.43 times higher risk of developing depression than OC-users (Duke et al., 2007). Interestingly, the Survey 3 data showed an increase in depressive symptoms in women that used OCs for reasons other than contraception (1.32 times higher risk). They concluded that although some association seemed to exist between OC use and depression, after adjusting for confounding variables, the association was no longer statistically significant. They acknowledged that there may be variation in the type of OC (monophasic or triphasic and estrogen/progesterone dosages) and its

influence on mood. Triphasic contraceptives and OCs with higher doses of estrogen and progesterone have resulted in more negative mood effects than monophasic or lower dose OCs. They hypothesized that if monophasic OCs were more popularly used by the women in this sample, then there could be a reduced association with depression than is actually present in the general population (Duke et al., 2007).

Total years of ever using oral contraception, by depressive symptom status, for women on Survey 3, with the percentage of women experiencing depressive symptoms and with associated 95% CI

	Depressive symptoms			
	Yes	No	% Yes	95% CI
Years of oral contraception use				
≤1	203	461	30.5	27.1–34.1
2–3	298	704	29.7	26.9–32.6
4–5	283	828	25.5	22.9–28.0
6–9	551	1737	24.1	22.3–25.8
≥10	408	1169	25.9	23.7–28.0

Note that there were 847 missing values.
There was a statistically significant association ($\chi^2=8.7$, $p=.009$).

Figure 4. Results from an Australian study of depressive symptoms depending on the number of years of OC use (Duke et al., 2007). As years of OC use increase, the percentage of women reporting depressive symptoms declines. They note that there may be a plateau after 5 years of use.

The neurobiological mechanism of OCs shows connection between ovarian hormones, serotonin, and glutamate, despite the lack of conclusive evidence internationally for an increase in depressive symptoms after taking OCs. There seems to be more risk in younger populations of women (around age 16), when brain maturation combined with exogenous sex-hormone use can contribute to changes in affect. Most studies did not designate the type of OC (monophasic or triphasic), which should be controlled for due to mechanistic differences and the known increased risk of negative mood symptoms in triphasic preparations. Neurological, physical,

psychological, and emotional impacts of any scale must be studied to improve the safety and efficacy of this medication.

Psychotropic Drug Interactions

Women experiencing mental illness are at greater risk for incorrect, inconsistent, or non-use of contraceptives, leading to more unintended pregnancies among this group. One of the reasons for this disparity may be negative interactions between HCs and psychotropic drugs. Psychotropic drugs are substances that impact cognitive function, affect, behavior, and experience, like alcohol, nicotine, marijuana, caffeine, antipsychotics, and antidepressants. I'm going to focus on the interactions between antidepressants and HCs.

A comprehensive review of 18 studies (Berry-Bibee et al., 2016) examined the efficacy of HCs when used consecutively with medications used to treat depression and anxiety. Their findings suggested minimal concern for significant interactions between HCs and SSRIs, TCAs, and benzodiazepines, but they noted that some of these studies were of poor quality (assessed by study design, sample size, validity, and generalizability) and further directed research is needed. However, one good-quality study they reviewed demonstrated an decrease in clinical efficacy of bupropion (Wellbutrin, an NDRI) in COC users (Berry-Bibee et al., 2016). The proposed mechanism of action involves inhibition of an enzyme responsible for the hydroxylation of bupropion into its active metabolite. So, there are increased concentrations of the inactive form of the drug, which decrease the desired antidepressant effects. Overall, this review concluded there was little to no concern regarding the ability of psychotropic drugs to significantly inhibit the metabolic pathways of HCs (Berry-Bibee et al., 2016). If this was a larger concern, there

would be increased concentrations of steroid hormones in the body, which would cause contraceptive-related safety concerns.

Interactions between neuroactive steroids and OCs are also important to examine due to decreased GABA activity as a consequence of hormonal birth control. Neuroactive steroids are endogenous or exogenous steroids that alter neuronal excitability in the central nervous system and are involved in mood and learning via serotonin activity (Tuem & Atey, 2017). Proper functioning of neuroactive steroids requires them to be at normal level, and abnormalities to their concentration can result in neuroinflammation and development of affective disorders like depression and schizophrenia.

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain that reduces neuronal excitability through decreasing the likelihood of an action potential occurring. It also is important to the regulation of psychological phenomena and mental health issues like anxiety, depression, sleep, sexual behavior, seizures, and other cognitive functions (Rapkin et al., 2006). The $GABA_A$ receptor is the main site of action for many psychotropic drugs, and allopregnanolone, the metabolite of progesterone, positively modulates the activity of this channel (Rapkin et al., 2006). During OC use, progesterone production from the corpora lutea is suppressed due to the signaling changes that occur, and the synthetic progestins that are introduced to the endocrine system may differ in their effects on receptor activity in the central nervous system (Rapkin et al., 2006). Since $GABA_A$ receptor activity is being altered by the different metabolites of progestin, there could be psychological impacts in people taking hormonal birth control who have decreased amounts of in allopregnanolone in their blood. In fact, individuals with clinical depression who are being treated with antidepressant medications have decreased concentrations of neuroactive steroids in their blood plasma and cerebrospinal

fluid (Rapkin et al., 2006). This pharmacological relationship provides a model to evaluate the impact of neuroactive steroids on affective disorders like depression and anxiety, especially in women and people with ovaries who have family history of mood disorders or are currently experiencing mental health struggles.

Hormonal Contraceptives and Brain Structure

Sex differences in adult brain structure can cause sex differences in behavior (De Vries, 2004). Generally, women have larger grey matter volumes in the prefrontal regions and left hemisphere, whereas men have greater brain volume bilaterally in the anterior para-hippocampal gyrus of the cortex, cerebellum and the amygdala (Pletzer et al., 2010). Other structural differences are currently being studied, especially with regards to hormonal impacts.

A high-resolution imaging study (Pletzer et al., 2010) examined the brains of 14 men, 14 women who were non-HC users, and 14 women who were current HC-users (note: this study considered all HCs, not just OCs). Women using HCs had larger grey matter volumes compared to naturally cycling women (not using HCs) in specific areas of the brain including the prefrontal cortex, the pre- and postcentral gyri, the para-hippocampal and fusiform gyri and temporal regions, during both the early follicular phase and mid-luteal phase (Pletzer et al., 2010). Additionally, naturally cycling women in the follicular phase had significantly larger grey matter volumes in the right fusiform and para-hippocampal gyrus than naturally cycling women in the mid-luteal phase. The affected regions are associated closely with memory and may have further impacts on behavior and physiology. For instance, in fMRI studies on humans the fusiform and para-hippocampal gyri have been implicated by the estrogen (and grey matter volume) decrease during and after ovulation, impacting spatial navigation abilities (Pletzer et al., 2010) (see Figure

5). The volume decrease found in these regions could cause impaired spatial navigation during ovulation.

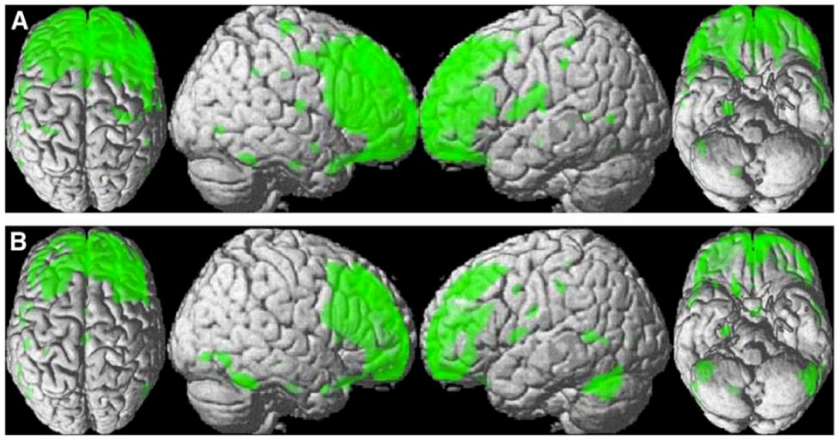


Figure 5. High resolution-VBM images comparing grey matter volumes between naturally cycling women and women using HCs (Pletzer et al., 2010). Differences in affected regions between early follicular phase (A) and mid-luteal phase (B) could reflect differing estrogen and progesterone levels. The use of OCs showed a greater difference in the follicular phase, indicating that increased exogenous concentrations of estrogen and progesterone during this phase of the cycle could have more of an impact on grey matter volume.

A recent review (Brønnick et al., 2020) assessed neuroimaging studies for the effects of HCs on the brain. In the literature, they found significant structural changes in the brain between naturally cycling women and those taking hormonal birth control. Notably, there was decreased reactivity in the left middle frontal gyrus (literacy) and left insula (visceral-sensory processing) and an increase in depressed mood, fatigue, and mood swings in the HC group compared to the placebo group (Brønnick et al., 2020). Altered amygdala activity was identified in another study (Gingnell et al., 2013) where women on HCs had lower amygdala reactivity after being presented with emotionally arousing images. The amygdala is the emotional association area, and modifications to this region can result in different reactions to sensory stimuli and lessened

perceived fear or other emotions that help humans adapt to their environment. Decreased emotional reactivity could be a consequence (or benefit, depending on the individual) of taking OCs.

In summary, HCs can alter brain structure, particularly in the regions modulating cognition, social behavior, emotional reactivity, and memory. More neuroimaging studies are needed to identify the physiological and behavioral implications of these brain changes.

Discussion

There is a lack of consensus on the influence of OCs on affective disorders. This dispute makes this topic extremely relevant at this moment in history when reproductive rights are being restricted across America. At least half of the population does not have free access to safe abortion and full individual reproductive freedom. This pertains especially to minority groups like people of color, transgender folks, and people in communities with less resources. Some studies have shown a significant relationship between depression and OCs (de Wit et al., 2020; Gingnell et al., 2013), and others have found the exact opposite (Duke et al., 2007; Lewandowski et al., 2020; O'Connell et al., 2007). One of the likely causes for this scientific disagreement concerns the role of estrogen and progesterone and the mechanism of affective disorders. Estrogen can be neuroprotective, but increased progesterone concentrations can contribute to higher levels of monoamine oxidase enzymes and therefore lower serotonin and dopamine levels in the synapse. Differing concentrations of estrogen and progesterone in birth control like OCs can contribute to distinct side effects.

People taking OCs have a higher likelihood of simultaneously reporting concurrent depressive symptoms and are also more likely to be on antidepressants for psychiatric treatment

(de Wit et al., 2020). More sensitivity is needed in clinical care to look further at possible drug interactions. Reproductive-aged women, especially adolescents, are seemingly more vulnerable to developing an affective disorder, and there is not yet a conclusion on why this is – could it be the prevalence of exogenous hormones like OCs? Or increased societal pressures compared to men? More research is needed in this field to better understand the interactions between HCs and affective disorders. Discrepancies exist because affective disorders are difficult to study due to individual variation in symptomology. Continuing to conduct large scale, inclusive, consistent psychological and neurobiological research is the way to breach these discrepancies and eventually reach a scientific conclusion.

Reproductive-aged women who are offered and encouraged to begin birth control sometimes do not receive proper, unbiased, patient-centered contraceptive counseling (*Patient-Centered Contraceptive Counseling*, n.d.). Being accurately informed of the potential side effects and social, sexual, mental, and behavioral changes that can occur from HCs should be a major part of informed choice when considering hormonal birth control methods. Other types of clinically administered hormone therapies, such as gender affirming hormone therapy (GAHT) or estrogen treatments for peri- or post-menopausal women are treated with much more discernment. Individuals seeking GAHT are often denied, questioned, or put through months of psychological testing, counseling, and other clinical care to assess their mental and physical wellbeing before hormone treatment is administered. Access to proper and safe healthcare for transgender folks is not trivial, as this is a vulnerable group of the population that undergoes extreme social pressures and judgement for their identity and gender expression in comparison to people who are cisgender. Common barriers to GAHT and other treatments such as chest

reconstruction, vaginoplasty, and puberty blockers include lack of information, systemic bias in the medical field, financial issues, and need of parental consent for minors (Puckett et al., 2018).

In contrast, hormonal birth control is given out relatively liberally – which I believe is a good thing, since it gives women more control over their fertility – but starting OCs or other forms of hormonal contraception without understanding the potential impact on one's brain structure and psychosocial behavior is an issue. For instance, there are long-term risks of OC use, including an increased risk of breast cancer, especially when OC/COC use began before the first pregnancy and treatment was started before 20 years of age (Schüler-Toprak et al., 2017). Mental health effects and affective changes, increased cancer risk, and other side effects of OCs must be treated as seriously as the similar side effects associated with GAHT and estrogen-replacement therapy. Perhaps more knowledge before beginning hormonal contraception could improve informed choice and provide patients with more security and comfort in understanding the changes going on in their bodies after taking this medication.

A major factor in giving women sexual freedom is the ability to be on birth control and understand how this kind of hormonal treatment may impact their physiology and behavior. Since women bear the physical effects of child-rearing, the possibility of getting pregnant at an inconvenient time in their life can be a huge stressor. In the United States, approximately half of all pregnancies are unplanned and accidental (Skracic et al., 2021). Unintended pregnancies are associated with poor economic stability and negative health outcomes for the mother and the child (Skracic et al., 2021). Abortions and emergency contraception are vital to maintain the health and wellness of women worldwide. Beginning in the 1960s, the feminist movement, which challenged traditional gender roles, was coupled with a sexual revolution in which women fought for their right to sexual pleasure (*The Pill and the Sexual Revolution | American*

Experience | PBS, n.d.). For much of human history, men were seen as the only gender with sexual needs, and the notion of women engaging in premarital sex was viewed as taboo and promiscuous. Conservatives blamed the pill for the sexual revolution that allowed women to separate sex from copulation. The introduction of the birth control pill encouraged pregnancy prevention, keeping women in the workforce, and gave women more power over their bodies and lives. Since the pill is almost 100% effective, women can control their own fertility and lifestyles, and have sex with any person at any time without the risk of pregnancy (*The Pill and the Sexual Revolution | American Experience | PBS*, n.d.).

The method of contraceptive use (or non-use) is directly correlated to the chance of a pregnancy occurring (see Table 1 for more details on contraceptive efficacy). Interestingly, the power dynamic between people engaging in heterosexual intercourse can contribute to the likelihood of contraceptive use. For example, women experiencing intimate partner violence are less likely to use any form of contraception (Skracic et al., 2021). Furthermore, 8.4% of women aged 18 and older in the United States have experienced reproductive coercion, which is where a partner controls a pregnancy outcome or tampers with or discourages methods of contraception to promote pregnancy (Skracic et al., 2021). On an individual level, in relationships, and under the law, rights to bodily autonomy in reproduction are threatened.

Currently, there are many barriers to access in contraception and disparities are prevalent worldwide. According to 2009 data, the percentage of women aged 15-49 who use contraceptives varies globally. 72.4% of women in more developed countries reported contraceptive use, but that percentage dropped as low as 31.4% in less developed countries (Christin-Maitre, 2013). Importantly, in 46 countries, approximately 20% of women of reproductive age have an unmet need for contraception. It is not a secret that accessibility issues

exist, especially when pertaining to healthcare. Medical procedures like IUD implantation or sterilization are expensive, age-limited, and sometimes not affordable to the general population in the same way that the pill can be acquired and easily taken orally. As the most common form of hormonal contraception, it is important to keep the pill available and affordable and simultaneously increase awareness of mental health effects that can occur as a result. Medication and treatment costs money, and communities with fewer resources may have decreased access to contraceptives, abortion, and mental health care. Now is the time to be proactive and progressive in reproductive research and improve global access to reproductive healthcare to improve contraceptive methods and the wellbeing of all people with ovaries.

Directions for Future Research

- Gathering data from populations that have been left out of science for decades; specifically, LGBTQIA+ folks and people of color. There must be more inclusive and diverse research to draw accurate and overarching conclusions that can benefit all groups no matter race, gender, or sexual identity. Diversity in scientific research, especially in neuroscience and psychology, is crucial because of the mental, emotional, and physiological consequences of generational trauma.
- Testing for genetic predispositions for specific mental health disorders like depression as well as measuring hormone levels could alleviate side effects of hormonal birth control. Knowing your individual biochemical and neuroendocrine make-up could influence which type of birth control your doctor prescribes. This is the kind of informed choice that is necessary to the future of reproductive healthcare.
- Research focused on teenagers would be valuable to the evaluation of affective symptoms since they seem to be the most vulnerable group. Studying mental health effects over time using positive or negative symptomology and quality of life measurements could provide insight to long-term consequences or benefits of OCs to that age group.
- Standardizing self-reported scores of depressive symptoms across studies on a global scale so results can be compared more accurately.
- Comparing depressive symptom increase or decrease over time in clinically depressed individuals and non-clinically depressed individuals by starting both groups on the same OC at the same time. This would measure the impact of the pill on different baselines of mental health issues.

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