Oral contraceptive use during brain development throughout puberty

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Abstract

Oral contraceptives (OCs) are one of the most prescribed types of medication worldwide. The rate at which they are prescribed to teenagers has increased over the last decade. During the teenage years, the brain goes through development to prepare for adulthood. This development in puberty is particularly sensitive to the sex hormones estradiol, progesterone, and testosterone. During puberty, these sex hormones exert activational and organizational changes in the brain. The organizational changes permanently determine certain behavioural responses to stimuli. OCs contain synthetic version of estradiol and/or progesterone and thus changes the normal hormonal environment.

So, how would OC use during puberty affect the hormone-sensitive brain development? The limited research studying the effect of OC use during puberty reports changes in brain structure and function, and stress reactivity. Pubertal OC use also increases the risk of antidepressant use, depression, and suicide attempts markedly. These results are worrying and should prompt some caution when prescribing OCs to teenagers. However, far more research has to be conducted to get a better picture of the effects on brain development and to be able to conclude if OC prescription to teenagers is harmful.

Contents

1. Introduction

Oral contraceptives (OCs), commonly known as “the pill”, are one of the most prescribed types of medication. Worldwide, an estimated number of 151 million persons used OCs in 2019 (Chadwick, Burkman, Tornesi, & Mahadevan, 2012; United Nations, 2019). Besides, the rate at which they are prescribed to young adolescents has markedly increased over the last decade (Rashed, Hsia, & Wilton, 2015; Ziller, Rashed, Ziller, & Kostev, 2013). The question is whether this is a good development. For example, a case was reported where an OC was prescribed to a 11-year-old girl, just 5 months following menarche (first occurrence of menstruation). Within a short period of time the girl started displaying symptoms of psychosis, although no history of personal or family psychiatric disease was known. She was taken off the OC followed by an improvement of symptoms. However, the symptoms did not disappear fully. Due to the very close temporal relationship the cause for the psychosis was traced back to the OC (Busby & Bancroft, 2007).

This case raises questions about the effect of OC use during puberty. Throughout puberty brain and body are being prepared for adulthood and reproduction. The brain development during this period is mediated by the sex hormones estrogens, progesterone, and testosterone (Vigil et al., 2011). OCs contain synthetic versions of estradiol and/or progesterone. These compounds change the internal hormonal environment and can possibly affect brain development.

For a long time, research focussed on the physiological side effect of OCs, e.g. cardiovascular side effects and breast cancer. Only in the last couple of years research broadened to studying effects on brain and behaviour. In even a shorter period, OC use during puberty is being researched, so information is limited.

In this review I will piece together the information that is available on OC use during puberty. First, I will explain the onset of puberty, the role of sex hormones therein, and the changes in brain and behaviour. Next, I will explain the use and mechanism of action of OCs. In the end I will conclude if OC use during puberty affects brain development, and if this is harmful to the user. I hypothesize that OC prescription during puberty is not in the best interest of the developing user, and that OCs should not be the first choice for contraception at these ages.

2. Puberty

Puberty and adolescence are often used synonymously; however, they are not the same. Puberty is the period of time in which an individual becomes sexually mature and entails the first years of adolescence. Puberty starts around the age of 10 years for individuals carrying two X chromosomes

(XX, from now on woman or girl), and ends at menarche around 12-13 years. Puberty starts and ends 1-2 years later for individuals carrying a X and a Y chromosome (XY, from now on man or boy). Adolescence starts at the same age as puberty but continues until psychological development is completed around the age of 21 years. Adolescence is a period of maturation on not only a sexual level but also on emotional, social, and cognitive levels (Vigil et al., 2011).

2.1. Puberty onset

The onset of puberty is determined by the metabolic resources in the body. The main metabolic resource determining onset is fat. Leptin, a hormone released by white adipose tissue (WAT, fat cells), is a signal of energy abundance. If leptin levels increase past a certain threshold, indicating adequate development, puberty is initiated (Garcia-Mayor et al., 1997). Ghrelin, a signal of energy insufficiency secreted by the gastrointestinal tract (GIT), is also thought to mediate puberty onset. Although the mechanism by which ghrelin acts is unknown, ghrelin is thought to be an inhibitory factor. Seeing that administration of 1nmol ghrelin for 10 days delayed vaginal opening (phenotypic marker of puberty onset in rodents) in female rats. (Roa et al., 2010) (see figure 1).

BOX 1| Secondary sexual characteristics

Boys:

- Growth of body hair
- Growth of facial hair
- Enlargement of Adam's apple
- Deepening of the voice
- Muscle development
- Broadening of shoulders
- Enlargement of penis and testes

Girls:

- Development of breasts
- Growth of body hair
- Widening of the hips
- Enlargement of labia minora
- Discoloration of labia minora

The onset of puberty is marked by the pulsatory release of gonadotropin-releasing hormone (GnRH) by the hypothalamus. Pulsatory GnRH stimulates the anterior pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the blood stream(Roa et al., 2010). FSH and LH stimulate the biosynthesis and release of the sex hormones estrogen, progesterone, and testosterone by the gonads, the primary reproductive organs (Roa et al., 2010).

However, GnRH neurons of the hypothalamus do not express leptin receptors, indicating leptin acts indirectly on theses neurons. On the other hand, neuropeptide Y (NPY) neurons in the hypothalamus do express functional leptin receptors. NPY neurons are thus thought to be the interneurons via which leptin acts on GnRH neurons. Indeed, knockout of the NPY receptor Y1 accelerated sexual development in response to leptin injections in rodents. This shows that NPY has an inhibitory effect on GnRH neurons. However, the fact that Y1 knockout alone was not enough to accelerate sexual development, and that leptin injections were necessary, indicates NPY is not the only mechanism implicated. There is an additional positive effect of leptin on the GnRH neurons (Gamba & Pralong, 2006). Kisspeptinergic nuclei in the hypothalamus also have functional leptin receptors. Binding of leptin increases the transcription of the kisspeptin-encoding gene. Kisspeptin can bind to receptors on neurons in the hypothalamus that steadily release gonadotropin-releasing hormone (GnRH). The binding of kisspeptin stops this steady release and starts the pulsatory release of GnRH to the anterior of the pituitary gland.

The surge in levels of the sex hormones triggers the development of secondary sexual characteristics (see Box 1). The development of secondary characteristics is used to assess maturation and physical development in adolescents participating in scientific studies with the Tanner scale (Marshall & Tanner, 1969, 1970). Besides physical developments, girls also undergo their first menstrual cycle.

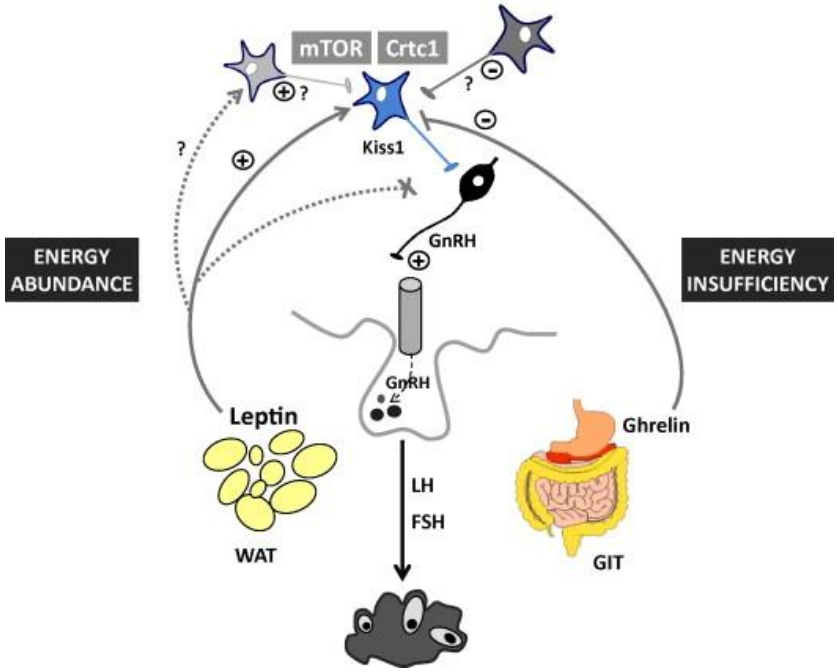

FIGURE 1| *Regulation of puberty onset by metabolic signals* (Roa et al., 2010)

2.2. The menstrual cycle

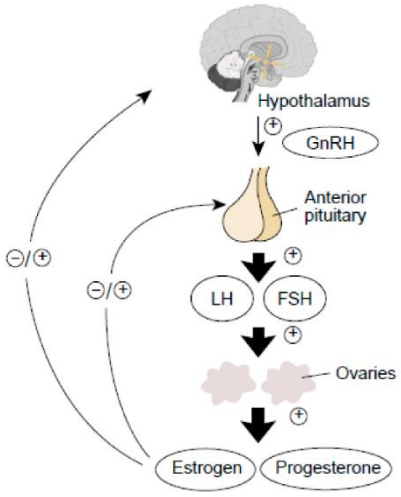

FIGURE 2| *The hypothalamic-pituitary-gonadal (HPG) axis. Edited from Kong, et al., 2014*

The menstrual cycle includes two eminent events, menses (bleeding) and ovulation (release of the egg from the ovaries). These events are regulated by the hypothalamic-pituitary-gonadal (HPG) axis (see figure 2). The first occurrence of menses in a girl's life is called menarche. The first day of menses indicated the first day of the cycle. A regular cycle varies between 20-35 days, averaging 28 days. The length of menses varies as well, but averages about 5 days. Ovulation occurs 14 before the end of the cycle, thus in an average 28-day cycle it occurs on day 14 of the cycle (Hampson, 2020).

The period from first day of menses to ovulation is called the follicular phase (see figure 3). During this period multiple follicles will develop, but eventually only is selected for ovulation. Involved in this selection process is the anti-müllerian hormone (AMH), which is secreted by developing follicles. AMH reduces the sensitivity of follicles to FSH (di Clemente, Racine, Pierre, & Taieb, 2021). When a follicle has developed past a certain size (8 mm) AMH secretion drops. Only the follicles past this size are now sensitive to FSH and start producing estrogen in response (Jeppesen et al., 2013). The rising levels of estradiol inhibit FSH release acting as a negative feedback signal. This stops the growth of the follicles. However, the biggest follicle with the most FSH receptors is able to survive and continue to grow with the limited amount of FSH available. This dominant follicle continues to release estradiol which now acts as a positive feedback signal on FSH and LH release. When the follicle is fully developed it releases sufficient estradiol to cause a surge in LH. This surge stimulates the release of the oocyte (egg) and thus ovulation (Rimon-Dahari, Yerushalmi-Heinemann, Alyagor, & Dekel, 2016). During the follicular phase increasing estrogen levels also stimulate the proliferation of the endometrium (the lining in the uterus) which was lost during menses (Dinh, Sriprasert, Williams, & Archer, 2015).

After ovulation, the luteal phase of the cycle starts. During this phase, the remnant of the follicle in the ovary, the corpus luteum (CL), releases estradiol and progesterone. Progesterone inhibits release of LH and FSH, and subsequently the release of estrogens. Progesterone also prepares the endometrium through differentiation for implantation of a fertilized egg. As the CL deteriorates estrogen and progesterone levels decline(Hampson, 2020). At the lowest level of progesterone, the endometrium begins to shed, marking the beginning of a new menstrual cycle (Dinh et al., 2015)

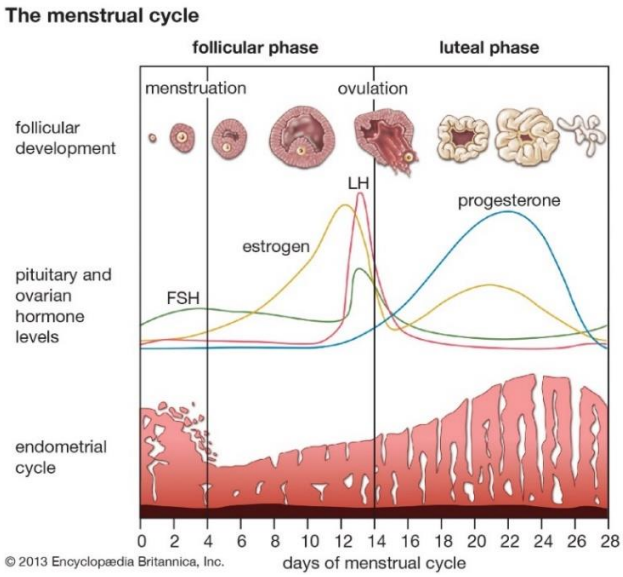

FIGURE 3| *The menstrual cycle. Depicting development of the follicle, hormone levels, and the development of the endometrium* ("Menstruation," n.d.)

2.3. Brain development

There are two periods in an individual's life wherein brain development is highly sensitive to sex hormones. The first period is during embryonic development and the second period is during adolescence. During both periods, each sex hormone exerts permanent organizational changes in the brain, which determine certain behavioural responses to stimuli (Scott, Stewart, & De Ghett, 1974; Sisk & Zehr, 2005).

Men and women have different levels of sex hormones causing them to develop differently. Both sexes have all three hormones in circulation, but at different ratios. The dominant sex hormone in men is testosterone, while the dominant sex hormones in women are estrogen and progesterone. The morphology of the brain thus varies depending on sex, which is termed sexual dimorphism (Vigil et al., 2011).

BOX 2| Organizational effects through:

Myelination = process of creating myelin, layers of isolation over neurons, thereby facilitating quick conduction of signals via the nerve. Gives the brain tissue a white appearance.

Neural pruning = process by which unused synapses in the brain are removed to maintain more efficient brain function.

Apoptosis = a form of programmed cell death.

Dendritic spine = protrusion from a neuron's dendrite that receives signals from axons at the synapse.

The effects of sex hormones on the brain can be divided into activational and organizational effects (see figure 4). Activational effects refer to sex hormones modifying activity of target cells and facilitating certain behaviour. They are short-term and change in accordance to changes in sex hormone levels. Organizational effects refer to the permanent morphological changes brought on by sex hormones (Sisk & Zehr, 2005). The changes come about through four mechanisms: myelination, neural pruning, apoptosis, and dendritic spine remodelling (Vigil et al., 2011) (see Box 2). Organizational

changes can be observed in brain structure e.g., grey matter and white matter volume, and brain function, among other things.

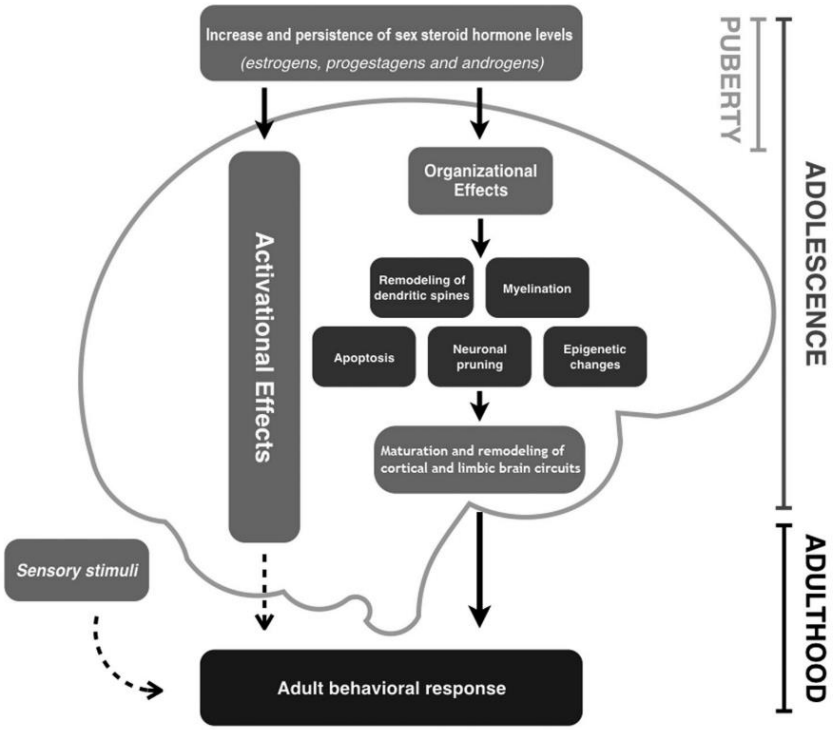

FIGURE 4|*Effect of sex hormones on the organization and activation in the brain during adolescence* (Vigil et al., 2016).

2.3.1. Grey matter volume

Changes in grey matter (GM) volume are one of the outcomes of the organizational effects brought on by sex hormones. The changes occur in an inverted U-shaped pattern; first volume increases up until early adolescence and then decreases throughout adolescence and adulthood (Giedd et al., 1999).

The peak and decrease of GM volume vary between regions and sexes. Girls typically peak earlier in overall GM volume than boys but have smaller GM volume up until the end of adolescence (Neufang et al., 2009). Multiple brain regions show sex dimorphism in GM volume, but the most prominent is seen in the putamen, insula, and amygdala. Boys show a smaller decrease in GM volume in these areas compared to a larger decrease in girls. On the other hand, boys show a larger decrease GM volume in the striatum and hippocampus compared to a smaller decrease in girls (Neufang et al., 2009; Peper et al., 2009).

How the sex hormones exactly affect GM volume is still in debate, but it is known they play a mediating role. Cross-sectional studies (Neufang et al., 2009; Peper et al., 2009) report a negative association between estradiol levels and overall GM volume and GM volume in the prefrontal, parietal, and middle temporal cortex in girls. In female rats prepubertal ovariectomy increased number of neurons and glia cells in the prefrontal cortex (PFC) (Koss, Lloyd, Sadowski, Wise, & Juraska, 2015). This indicates that the absence of estradiol stops pruning, and thus the importance of estradiol in the process. Positive correlations between estradiol and GM volume were found in the middle frontal-, inferior temporal-, middle occipital gyri (Peper et al., 2009), uncal cortex and parahippocampal gyrus (Neufang et al., 2009). Testosterone was positively correlated with GM volume in the amygdala and diencephalon (hypothalamus, ventral thalamus) and negatively correlated with GM volume in the hippocampus, precuneus, and superior parietal gyrus. No correlation was found between testosterone and overall GM volume in girls (Herting et al., 2014; Neufang et al., 2009).

2.3.2. White matter volume

On the contrary to GM, white matter (WM) volume increases with a steady rate as a result of organizational changes. Boys show a larger increase in WM volume than girls (Herting et al., 2014). The increase in WM volume is attributed to myelination induced by the sex hormones. LH also seems to have an influence on WM volume, since a positive correlation was found with WM volume in the cingulum, splenium of the corpus callosum, middle temporal and right superior frontal gyrus (Peper et al., 2008). A positive association of testosterone with WM volume of the precentral gyrus was found. A negative association of estradiol with WM volume of the fractional anisotropy of the right angular gyrus and the superior longitudinal fasciculus was found (Herting, Maxwell, Irvine, & Nagel, 2012).

2.3.3. Cortical thickness

Changes in cortical thickness is also reported as a result of organizational changes. In girls estradiol levels are negatively correlated with middle temporal lobe thinning (Herting, Gautam, Spielberg, Dahl, & Sowell, 2015). Testosterone levels are negatively correlated with cortex thickness in the occipital lobe in girls. Interestingly, in boys testosterone has the opposing effect, as it is positively correlated with cortex thickness in limbic and primary sensory cortices of the occipital lobes (Bramen et al., 2012). In female rats prepubertal ovariectomy had a greater volume of cortical matter (Koss et al., 2015), indicating absence of sex hormones stops cortical thinning.

2.3.4. Functional changes

The increase and persistence of sex hormone levels also effect functional changes associated with socio-emotional development. Levels of sex hormones are positively correlated with brain activity in the anterior temporal lobe, during a socio-emotional processing task (Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012). This region is involved in processing social emotions like guilt and embarrassment.

Sexual dimorphism is seen in brain connectivity as well, with greater between-network connectivity in boys, and greater within-network connectivity in girls (Satterthwaite et al., 2015). Sexual dimorphism is also found in the connectivity of the default mode network (DMN). Maturation is associated with weaker connectivity in the DMN in girls, and stronger connectivity in boys. The DMN includes the anterior medial PFC, posterior cingulate cortex, middle temporal cortex, and hippocampus. It is thought that changes in the DMN play a role in the development of psychopathologies like internalizing behaviour during adolescence (Ernst et al., 2019). Also, increased connectivity in the salience network (SN, insula and dorsal anterior cingulate cortex) in girls is associated with depression-like behaviour (Ordaz et al., 2017).

2.3.5. Stress reactivity

Adolescence is not only a period of the HPG-axis, but also of the hypothalamus-pituitary-adrenal (HPA) axis. In this axis external and internal stressors are relayed to the hypothalamus which releases corticotrophin releasing hormone (CRH) to the anterior pituitary. The pituitary then releases adrenocorticotrophic hormone (ACTH) into the bloodstream in response. In turn, ACTH causes the secretion of glucocorticoid hormones (cortisol in humans, corticosterone in rodents) from the adrenal cortex into the bloodstream. During adolescence basal cortisol levels increase. A study using CRH to stimulate ACTH secretion in adolescents reported maturation resulted in an increased ACTH response in girls compared to boys (Stroud, Papandonatos, Williamson, & Dahl, 2004). Before a public speaking task and a mental arithmetic task basal cortisol levels were higher in later adolescents compared to early adolescents. After the tasks in particular 13-year-old girls exhibited greater cortisol responses than age-matched boys (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). These results suggest that girls display age-associated increase in basal activity of the HPA-axis and stronger stimulated stress response during puberty.

2.4. Behavioural changes

Adolescents also undergo changes in their behaviour that disappear after transitioning into adulthood. Adolescents are often characterized as egocentric, and often behave erratic, impulsive, and irrational. These behaviours are explained by the still developing cortical-limbic system. The cortical regions act as a filter of stimuli coming in from the limbic system. They inhibit stimuli of risky behaviour and favour behaviours that lead to fulfilment. During adolescence, the activity of the limbic system far exceeds the activity of the cortical system, and inhibition is lacking due to immature cortical regions. Thus, explaining the predominance of emotional, impulsive behaviours exerted by adolescents. So, due to ongoing development of brain circuits teenagers have limited abilities to recognize wrong information or to stay interested in and motivated by future rewards in contrast to immediate reward (Vigil et al., 2016).

In this chapter on the subject of puberty, we have discussed sex hormones and their effect. We also discussed their fluctuations throughout the menstrual cycle in girls and women. Now we will continue with oral contraception and how it intrudes on hormonal fluctuations.

3. Oral contraception

Oral contraceptives (OCs) came to the market for the first time in 1961. The medication was developed under pressure of feminist and founder of Planned Parenthood Federation of America (PPFA) Margaret Sanger. First experiments with the progestin (synthetic hormone with progestogenic activity) norethynodrel were successful. However, a more purified version of norethynodrel caused much breakthrough bleeding. It was discovered that the original medication was contaminated with mestranol, a synthetic estrogen. Combining both compounds led to the first combined oral contraceptive (COC) Enovid®. Later ethinylestradiol (EE) replaced mestranol. And, in the following years hormonal dosages were reduced, new progestins were introduced, and new administration schemes and routes were created to reduce side effects (see box 3) while maintaining effectiveness (Marc Dhont, 2010). Now, combined hormonal contraception methods include the COC, vaginal ring, and transdermal patches. Progestogen-only methods were developed as well, including the progestogen only pill (POP), also called the “mini-pill”, hormonal intrauterine systems (IUSs), injections, and implants (David et al., 2006).

BOX 3| Side effects of OC use

Severe:

- Thrombosis
- Pulmonary embolism
- Psychological problems
- Serious cardiovascular disease
- Stroke
- Breast cancer
- Cervical cancer

Non-severe:

- Headache
- Dizziness
- Breast tenderness
- Nausea and vomiting
- Breakthrough bleeding
- Decreased libido
- Mood swings
- Weight gain
- Vaginal infection

3.1. Oral contraception use

Of all the contraceptive methods available OCs are still the most widely used throughout the world. In 2019 ~70.5% of contraception users in the Netherlands used COCs, and after including the POP the percentage of OC use increased to ~73.3% (“Bijna miljoen gebruiksters eerste keus-anticonceptiepil,” 2020).

In the last years, OCs are being prescribed to teenagers to a greater extent. In multiple European countries the percentage of COC prescriptions for girls between 16-18 years increased, and even percentages of girls between 12-15 years increased significantly (Rashed et al., 2015; Ziller et al., 2013).

These girls were not only prescribed OCs for contraceptive use, but also for a multitude of other reasons (M Dhont & Verhaeghe, 2013) (see box 4).

OCs are 99.7% effective at preventing pregnancy, however with "typical use" this percentage drops to 91% (Trussell, 2011). This is because OC use is affected by consumer failure. For OCs this could mean missing a pill, not taking the pill consistently at the same time every day, vomiting within 3 hours after oral ingestion, or severe diarrhoea.

BOX 4| Indications for off-label OC use

- PolyCystic Ovary Syndrome (PCOS)
- Endometriosis
- Painful menstruation (dysmenorrhea)
- Acne
- Excessive growth of coarse hair in a male-like pattern (hirsutism)
- Heavy menstrual bleeding (menorrhagia)

3.2. Mechanism of action

One strip of COCs contains 21 pills which are taken on consecutive days followed by 7 pill-free days. During the pill-free week bleeding occurs. Other types of COCs contain 7 placebo pills or changing dosages of estradiol and progestins. The latter, called multiphasic COCs, mimic natural fluctuations in hormone levels during the menstrual cycle. The most common COC is a combination of a steady dose of 15-35 µg EE and levonorgestrel or any of 12 progestins depending on the brand (Hampson, 2020).

The primary mechanism of action of COCs is the prevention of ovulation through disruption of the HPG-axis. The synthetic estradiol and progestins inhibit the secretion of FSH and LH by the anterior pituitary (Marc Dhont, 2010). The synthetic sex hormones act onto the hypothalamus where progesterone and estrogen receptors (ERs) are bound by their synthetic ligands. FSH and LH levels are decreased within the first day of oral ingestion of COCs, which leads to decreased secretion of hormones by the ovaries. Consequently, serum levels of endogenous hormones estradiol, progesterone and even testosterone are low during COC use. These concentrations mimic serum levels during menstruation in a normal menstrual cycle when hormone secretion by the ovaries is low (Hampson, 2020).

Beside the prevention of ovulation, COCs have additional contraceptive effects. Firstly, under influence of progestins cervical mucus thickens at the entrance of the uterus, making it less hospitable for sperm. Secondly, the proliferation of the endometrium is stopped, possibly making implantation of a fertilized egg much more difficult. Progestins down-regulates the ERs after several cycles, reducing the proliferative effect of estradiol on the endometrium (Dinh et al., 2015).

3.3. Oral contraceptives in the brain

Not only serum levels of estradiol, progesterone, and testosterone decrease during COC use. COCs also seem to decrease concentrations within the brain. This was reported by numerous rat studies (Porcu, Serra, & Concas, 2019). Even in ovariectomized rats brain concentrations of the sex hormones were decreased by OCs, suggesting a direct effect of OCs on the synthesis of neurosteroids (sex hormones produced in the brain)

Estradiol and progesterone synthesized intra-neuronal have beneficial effects including neuroprotection, mood enhancement, and modulation of neuronal plasticity and cognition. Progesterone and its active metabolite allopregnanolone exert neuroprotective effects, and increased biosynthesis may be part of this mechanism after injuries (Guennoun et al., 2015). Estradiol synthesized intra-neuronal may contribute to learning and memory and may also improve the cognitive response to stress (Luine, 2014). So, the decrease of the neurosteroids due to OCs could affect normal brain function.

There is also evidence of OCs affecting neurotransmission by monoamines, γ-aminobutyric acid (GABA), and neuropeptides like brain-derived neurotrophic factor (BDNF). OCs increase levels of serotonin and its precursor tryptophan and decrease dopamine levels. Moreover, OCs inhibit transporters of serotonin and dopamine, and the metabolizer monoamine oxidase. OCs also increase GABA levels in the brain and alter the expression of the GABA receptor subunits. The latter is possibly mediated by the positive endogenous modulator of GABA receptors allopregnanolone. OC use even reduces

BDNF in the hippocampus. BDNF is important for long-term potentiation in the forming of long-term memory and cognition. Lastly, OCs increase expression of the galanin peptide, stress-inducible and co-transmitter in serotonergic and noradrenergic neurons. Galanin possibly inhibits noradrenergic transmission, which is a mechanism thought to be linked to changes in cognition and anxiety induced by EE (Porcu et al., 2019).

4. Oral contraceptives during adolescence

In this chapter I will assemble the research that was conducted on OC use during adolescence. Research into the effect of OCs on the developing adolescent brain has only recently started to dawn. Mostly for the reason that for a long time (neuro)scientists believed sex influences did not matter outside the reproductive function. Adding to this is the fear of studying sex differences due to concern of being accused of thinking women and men inequal. However, the fact that women and men are equal does not mean they are the same (Cahill, 2014).

4.1. Adolescent OC use in humans

Studies performed with humans consisted of cross-sectional (functional) magnetic resonance imaging ([f]MRI) studies or large cohort studies, which compared OC users and former OC users to normal cycling (NC) women.

4.1.1. Altered brain structure

In the first study the differences in brain structure and function between OC users and NC women were investigated. OC users were divided into pubertal-onset (PO) and adult-onset (AO) users. PO users began within 6 months following menarche and AO users began after turning 18 years of age. 75 women (12 PO, 15 AO and 48 NC) were recruited for fMRI sessions. Ages ranged between 18 and 26 years.

OC users showed greater decrease in GM volume (right putamen) compared to a small decrease in NC women. OC users also showed a greater increase in WM volume (right putamen, right rectus, right amygdala, left parahippocampal gyrus, and left hippocampus) compared to a smaller increase in NC women. PO users showed a greater increase WM volume than AO users in the left fusiform gyrus and right precuneus, and also greater activity was measured in these regions (Sharma, Smith, et al., 2020).

4.1.2. Altered brain function

In the same study participants were asked to perform a memory task during the fMRI session. They were shown either neutral, positive, or negative images, and were asked to either push “1-Back” (baseline memory) or “2-Back” (working memory) when they recognized an image seen 1 or 2 images prior in the sequence. The duration of use among PO users was positively correlated with activity in multiple regions. The fact that OC users showed increased brain activation in response to negative images compared to NC women, together with other research, suggests OC causes emotional sensitivity to negative stimuli (Sharma, Smith, et al., 2020).

In another article they reported on alterations in resting state functional activity in these women. For 5 minutes brain activity was measured using fMRI while the women were instructed to “relax and try not to think of anything in particular”. OC users, especially PO users, showed increased connectivity in the SN compared with activity in NC women. Like mentioned before, greater connectivity in this region was linked to depression-like behaviour in adolescent girls (Ordaz et al., 2017). OC users in general showed greater connectivity in the central executive network (CEN), reward network, and subcortical limbic network than NC women. OCs could alter neuronal pruning and apoptosis during

adolescence resulting in greater resting state activity in the SN of OC users compared to the activity in NC women (Sharma, Fang, Smith, & Ismail, 2020).

In 110 adolescent girls (55 NC, 55 OC) an alteration in brain response to faces was reported. Women in general tend to have a stronger activation than men in numerous cortical areas, including the fusiform face area (FFA), in response to emotional ambiguous faces. In response to images of angry faces, adolescent OC users showed a greater increase in activity in right caudate and right thalamic region compared to a smaller increase in activity in NC adolescent girls. Adolescent OC users also showed a greater increase in mean activity in the left FFA to the ambiguous pictures compared to the smaller increase in NC girls. This greater increase in activity during face perception and emotion recognition might indicate enhanced processing of social cues in adolescent OC users (Marečková et al., 2014).

4.1.3. Altered stress reactivity

In the first mentioned study in this chapter 140 additional women (26 PO, 36 AO and 82 NC) were recruited for stress testing. They were subjected to social stress test, which consisted of 5 minutes of public speaking and 5 minutes of mental arithmetic tasks in front of a panel of judges. Salivary cortisol was taken and measured before public speaking, after the tasks, and 20 minutes after end of the test. They also filled in the visual analog scale for subjective stress response, the State Trait Anxiety Inventory, and the Beck Depression Inventory. PO users had a significantly greater decrease in cortisol response after the tasks and 20 minutes after the test compared to the smaller decrease in AO users. Also, in the group of PO users there was a markable higher percentage of participants not responding with increases in cortisol (AO: 47% cortisol non-responders, PO: 81% cortisol non-responders). This does suggest an effect of PO OC use on stress reactivity causing a blunted cortisol response (Sharma, Smith, et al., 2020). Blunted stress reactivity can be a risk factor for developing depression (Fiksdal et al., 2019). Not only the HPG-axis matures during adolescence, but also HPA axis develops during this time (Gunnar et al., 2009; Stroud et al., 2004). So, OC use during adolescence could alter HPA-axis development possibly increasing risk of developing pathologies. Although, one could argue that the decreased stress response could be due to conditioning to public speaking and the arithmetic tasks since such tasks are performed during the education of these adolescents.

4.1.4. Vulnerability to depression and suicide

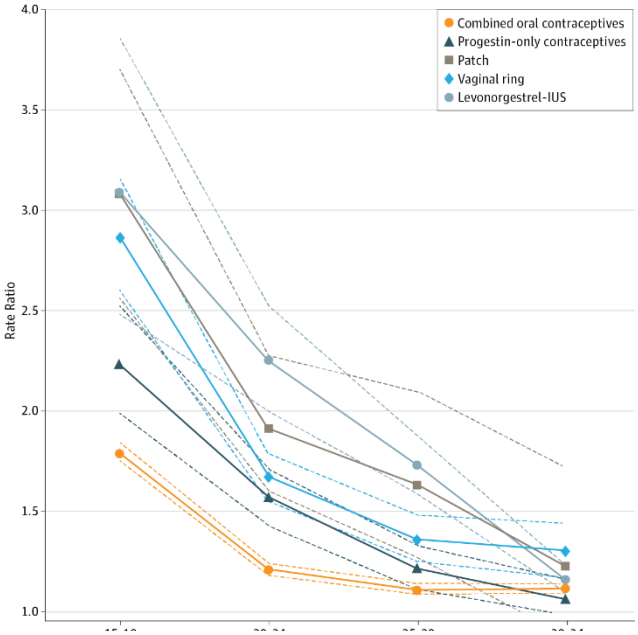

FIGURE 5| *Rate ratios of first prescription of antidepressants per age group per contraceptive type (Skovlund, et al., 2016).*

Two nationwide cohort studies by Skovlund, et al. investigated whether the use of hormonal contraceptives is associated with antidepressant use, diagnosis of depression, suicide, and suicide attempts. They made use of The Danish Sex Hormone Register Study which includes over 1 million women living in Denmark and combined this with the National Prescription Register and the Psychiatric Central Research Register. Women with prior antidepressant use, psychiatric, cancer, or venous thrombosis diagnoses were excluded. They found that the use of COCs experienced an incidence rate ratio (RR) of first antidepressant use of 1.2 (NC women as reference). For adolescent COC sue RR was notably higher, namely 1.8, however RRs of other hormonal contraceptives were even greater (see figure 5).

Relative risk peaked after 6 months of use with an RR of 1.4 for antidepressant use, and an RR of 1.5 for first diagnosis of depression. Also, the age at which COC use was initiated had a notably effect on first antidepressant use. Adolescents starting COC between 15-19 years of age had an RR of 1.8, compared to an RR of 1.4 when COC use started between 20-30 years of age (Skovlund, Mørch, Kessing, & Lidegaard, 2016).

Using the same Denmark database and exclusion rules the researchers found that relative risk of suicide attempt increased rapidly after initiation of hormonal contraceptives depending on age of first hormonal contraceptive use. Relative risk peaked after 1 year but remained higher compared to NC women for more than 7 years. RRs were at 2.06 for 15–19-year-old women, 1.61 for 20–24-year-old women, and 1.64 for 25–33-year-old women. The use of COCs had an RR of suicide attempt of 1.91 (Skovlund, Mørch, Kessing, Lange, & Lidegaard, 2018).

A study performed with data from 1,236 women from the USA reported that the effect of OC use during adolescence was not only short-term, like reported above, but also long-term. The women were divided into groups of PO users, AO users (both including former users) and NC women. The prevalence of depression over a period of 12 months during adulthood was assessed using the World Health Organization Composite International Diagnostic Interview. Prevalence of depression in adulthood among the AO users was 16.1%, while for AO users this was 9.3%, and NC women 5.7%. Controlling for current use did not alter the odds ratio significantly. So, women who started using OCs during adolescence were at a higher risk of developing depression in adulthood even when controlling for current use (Anderl, Li, & Chen, 2020).

These studies have adjusted for many covariate factors. These included age at menarche, age at sexual debut, education, marital status, BMI, diagnosis of endometriosis, diagnosis of PCOS, ever use of other medication containing female hormones such as oestrogen and progesterone, pregnancy in the past year, smoking history, sex of sexual partners and current OC use. Other factors like age, poverty income ratio, ethnicity, ever use of Depo-Provera or injectables to prevent pregnancy and total duration of lifetime OC were not included as they were unrelated (Anderl et al., 2020; Skovlund et al., 2018, 2016). Also, personality was not included in the factors. One could argue that personality characteristics could be associated with pill use. However, a study investigating the Big Five personality factors in OC users and NC women reported no personality differences between the groups, suggesting that reported differences may be linked to neuroendocrinology and not personality (Beltz, Loviska, & Kelly, 2019).

4.2. Adolescent OC use in rodents

To test the effects of OCs during puberty on the brain in experimental animals, female rats were given either an oral dose of EE dissolved in peanut oil (EE group) or peanut oil (OIL group) at clinically relevant doses. The rats were treated during their early pubertal phase (postnatal day [PND] 23-30, puberty = PND 28-42). On PND 37 and PND 90 animals were sacrificed for immunohistochemical staining of ERs in multiple hypothalamic areas. Number of ERs in the arcuate nucleus of the hypothalamus were increased in the EE group compared to no increase in the OIL group, but this effect was not long-term. No short-term or long-term changes were found in the ventromedial nucleus. However, in the medial preoptic area (MPA) the EE group had significantly more ERs than the OIL group at PND90. The MPA includes the sexual dimorphic nucleus in rodents and is involved in female reproductive behaviour, mediating receptivity and motivation (Ceccarelli, Seta, Fiorenzani, Farabollini, & Aloisi, 2007).

A study looking into the effects of OCs on sexual behaviour, exposed female rats to EE for a prolonged period including puberty. Behavioural testing at PND 90 showed a significantly decrease in receptive behaviour (acceptance of coital activity with a male) in the EE group compared to no decrease in the OIL group. Proceptive behaviours (solicitation of a male's sexual attention) were also significantly decreased in the EE group compared to no decrease in the OIL group. Additionally, non-

receptive behaviours like exploration and aggression were increased in the EE group compared to no increase in the OIL group. These kinds of behaviours are typical masculine during a male-male encounter. The change in behaviour could be due to EE permanently altering the MPA (Della Seta, Farabollini, Dessì-Fulgheri, & Fusani, 2008).

5. Conclusion

From this review we can conclude that puberty and adolescence are periods of great sensitivity to sexual hormones and that the development occurring during these periods is dependent on the sex hormones. We can conclude that OCs alter the hormonal environment within the women's body and can enter the brain where they can exercise multiple effects. And finally, that OC use during adolescence increases, and that OCs in this period exercise effects in a greater magnitude and longevity than in other periods in life. However, we are unable to label the alterations in brain structure and functionality by OCs as negative effects. Also, the alterations in brain structure and connectivity reported could either be from adolescent OC use or long-term use. Namely, PO users had an average time on OCs of 73.0 months while AO users only had an average of 20.4 months (Sharma, Smith, et al., 2020).

With the information contemporarily available the major concern lies with the OC and depression correlation. Adolescents, especially adolescent girls, are more sensitive to emotional stimuli, and they already are at increased risk of developing affective disorders. Adolescent OC use seems to increase sensitivity to emotional and negative stimuli. Plus, adolescent OC use also increases connectivity in the SN which is linked to depressive-like behaviour. This could contribute to the development of depression of which the short-term and long-term risk is markedly increased during adolescent OC use. Thus, considering that OC use almost doubles the risk of antidepressant prescription within 6 months after initiation, the increase in OC use among teenagers should be looked at with a minimum of concern.

Knowing that during adolescence the brain is particularly sensitive to sex hormones and developing according to their influence, the lack of knowledge of OC use during this period is astounding. Just 3 years ago a review by Cahill touching upon hormonal contraception affecting brain development was only able to find 1 study that controlled for adolescent hormonal contraceptive use (namely Marečková et al., 2014) (Cahill, 2018). Luckily, in 2021 we see a marginal increase in interest for this subject.

Steps should be taken to gain an actual understanding the mechanisms by which OCs exert their action on the brain development during adolescence. Animal models represent a valuable approach to investigate this. Some studies have used this approach already to study the brain as target for OCs (Porcu et al., 2019), however not during adolescence. Much of preclinical research performed in animals have actually focussed on OCs during the first developmental period sensitive to sex hormones, the perinatal period. So, I would urge the researchers in this field to also shift their focus to the other developmental period, adolescence.

Human research on OC effects on the brain, during adolescence or otherwise, is very heterogenous. For example, some report no effect on risk of depression or antidepressant use, while some report a protective effect. Both of which are in contrast with the research presented in the previous chapter. However, as Anderl, et al. observed, most studies did not differentiate between former users and never users and clustered them in one group of non-users. However, as Anderl, et al. reported former users can still experience the long-term effects of OC use, which possilby explains the neutral or postive effects reported(Anderl et al., 2020). So, further research should not group according to current OC use, but should group according to age of onset of OC use.

Until more is known about the effects of OCs on the brain, I do think OC prescription to teenagers should be considered with caution. Numerous alternative and non-hormonal treatments exist that could replace mediating OC use. For example, to treat acne practitioners can prescribe topical treatment creams like Benzoyl peroxide or Tretinoin (which localize treatment). Nowadays cosmetic brands manufacture very effective products to treat acne as well. If a teenager is looking for a contraceptive, I would advise to explore non-hormonal contraceptives before considering hormonal ones. Mechanical barriers like the condom are very effective and also reduce the transmission risk of sexually transmitted infections (Batár & Sivin, 2010). Although, this puts the responsibility on the other person. While the OC gave women control over their bodies and relief from unwanted pregnancies (Marc Dhont, 2010). Another option are intrauterine devices (IUD) like the copper IUD are very effective as well and can protect continuously for up to 10 years or longer (Sivin & Batár, 2010). This long continuous protection is resistant to consumer errors and could bridge the teenage years where pregnancy is most likely unfavoured. However, I would not urge the prescription to be suspended. For many teenagers with PCOS, endometriosis, very heavy and painful menstruation OCs are very effective at easing symptoms. In those cases, the benefits far outweigh the side effects.

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