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THE GREATEST HORMONAL EXPERIMENT EVER?

An interdisciplinary investigation into the influence of the birth control pill on women in
Western societies

Liberal Arts and Sciences Interdisciplinary Research Project

Period 1 – 2014/2015

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Chapter 1

Introduction

Every day millions of women around the world take a tiny pill to prevent them from becoming pregnant. Ever since the invention of the Combined Oral Contraceptive pill in the 1960s, its use has been steadily increasing, up to currently being the third largest group of birth control methods worldwide (UN, 2011; Christin-Maitre, 2013). As of 2009, the pill constituted over 40 percent of all birth control measures taken in Europe, making it one of the largest and most long-lasting hormonal experiments ever conducted on any group of people. While some changes in its chemical compound have occurred over the years, in essence the pill has remained virtually the same in its biochemical workings, affecting females' sex-hormone levels and functioning in major parts of the population. Furthermore, the introduction of the pill has coincided and interacted with major societal changes such as the changing position of women, reflected for instance by the increase in female labor participation, and different societal attitudes towards sexuality and fertility. As the pill seems to impact the lives of so many individual women and society as a whole it seemed relevant to examine what the exact effects of the pill have been and whether

these effects have been mainly positive or negative.

The aim of this study is to answer that question by investigating current literature on the effects of the pill on individual women and society and evaluating whether these effects have been improving the lives of women. Effects of the birth control pill transcend the boundaries of single disciplinary perspectives as it influences women's bodies, behaviors, socioeconomic statuses and - through all the aforementioned - their position in societies at large. The phenomena affected by, and resulting from the use of the pill also interact with each other on various levels, turning the resulting research question in a complex one that makes an interdisciplinary approach necessary. Such an approach is needed as only integrating these different perspectives makes it possible to study the interaction between different phenomena which would remain unviewed in a merely disciplinary approach. In this research we sought an answer to our interdisciplinary research question:

To what extent has the birth control pill had a positive influence on women in western societies?

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We have chosen to focus on western societies, motivated by a number of factors. First, we consider the Western world a more homogenous cultural area, with relatively similar societal characteristics. This means that effects of the pill are most likely clearest observed in these regions, and due to the cultural similarities, comparisons on the societal level become possible. Besides this, choosing western societies also has pragmatic grounds as the amount of research available on these regions far exceeds that of any other region.

In order to answer the interdisciplinary research question we gathered insights from a multitude of academic disciplinary resources, compressed in three fields of research: biomedical studies, behavioral neurosciences and population studies. First of all, biomedical studies has provided crucial understanding of the biological workings of the birth control pill, which is an important step in understanding its other effects on the female body. We see that the pill influences women's natural hormone levels that regulate the menstrual cycle. The synthetic sex-hormones in the pill halt the ovulatory cycle, and so prevent women from becoming pregnant. However, changes in the body's natural hormone balances elicited by the pill cause multiple side-effects, among the affected is the immune system. As pill use increases risk of inflammatory diseases in

users, consequences for health and well-being can be severe.

Insights from the behavioral neurosciences tell us sex-hormones play an important role in the brain, with pill use influencing brain structure and functioning of its users. These findings concur with minor effects on the behavioral level. As we are just beginning to uncover the mechanisms that link the effects on brain and on behavior, research in this developing field is still amassing new insights that further advance our understanding. Most of the observed changes with regard to mental functioning (memory, verbal and visuospatial performance) are small and can be considered neutral by most society standards. Another aspect that is more troublesome is the fact that the pill can have a deteriorating influence on women's mood and handling of stress.

The effects of the pill are further determined by the way it is used and viewed in society. To take this into account we used insights from the population studies using knowledge gathered from various disciplinary resources (demography, human geography, economy). The main effect these studies observed, was that the pill allowed women to take birth control entirely into their own hands. This strongly improved their ability to plan childbearing, freeing women to invest more in their educations and careers. This led to higher female labor participation,

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influencing the position of women in society as it changed societal attitudes. However, as pill use was and is unequally distributed across various social classes, and even across societies, its benefits (and risks) are not shared by everyone.

We recognize that there are other research disciplines, such as for instance anthropology, gender studies or sociology that might have provided valuable insights on the topic of women's well-being. However, as we were limited in time and resources, we leave it to others to further explore those directions. The main goal of this study was to use insights from the different disciplines and integrate these into a more encompassing answer to (and doing justice to the complexity of) the research question. By doing so we also evaluate the effects of the use of OC since its introduction which might

be used by policy makers and individual users to form a better understanding of OC. We first present the insights gathered from the different fields of research separately. With every chapter we briefly describe the characteristics of that particular field and we give a short interdisciplinary analysis of the way the constituent disciplines conduct and view research. Thereafter we integrate the different insights into a single interdisciplinary framework and shape our new insights by formulating a number of hypotheses.

We conclude the pill has brought women increased social and financial freedom at the cost of increases in certain physical and mental health risks, and policy makers will have to continue monitoring whether the side effects will not outweigh future benefits.

Chapter 2

Biomedical Sciences approach

Disciplinary remarks

Health sciences comprise of a variety of scientific disciplines such as social- and biomedical sciences. Combination of these disciplines in scientific research provides a comprehensive understanding of the normal body functioning as well as the pathophysiology of diseases. In this section, we focused on the biomedical part of the question. Biomedical sciences (BMS) studies the biological processes of living organisms. It searches for physical and deterministic explanations of the functioning of the human body. BMS focus on the properties of molecules individually, in compounds, and their subsequent interactions. It sees larger-scale organisms in terms of their constituent elements and compounds. BMS integrates genetic factors, mechanisms, and chemical processes in the body; to understand its normal function, as well as its pathophysiology. BMS, on one hand endorses the value of classification, on the other hand, experimental control. The latter implies identifying causalities, which prefers experimental methods of research because of its replicability (Magnus, 2000).

The functioning of the organism is reducible to the properties and mode of actions of its constituent elements and their interactions. “All living organisms share certain chemical, molecular, and structural features, interact according to well-defined principles, and follow the same rules with regard to inheritance and evolution” (Donald, 2002). Thereby biomedical scientists use an approach of deductive reasoning based on a hypothesis, to derive explanations or predictions from laws in phenomena or processes, based on the principle of falsification (Quinn and Keough, 2002).

Basically there are three research methods used in BMS. First, observational/epidemiological research studies whether there is a statistical relation (association) between a determinant and a (health) outcome. Examples are cross-sectional-, patient-control- and cohort research. Benefits of this method are that many variables can be included and a long period of exposure can be studied. Disadvantages are that a causal relation cannot be proved and there is risk of confounding, information- and selection bias.

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Second, randomized controlled trial (RCT) is an experiment based on manipulation by the researcher. It is designed such that it constitutes an intervention (experimental) group versus a control group. The control group ensures that the effect can be attributed to the intervention. The randomization results in similar groups, which ensures that the effect could not have been caused by another (prognostic) factor. Blinding prevents bias into the expected direction (placebo-effect). Possible designs are parallel and crossover. Advantages of this method are controlled exposure, the ability to prove causality and absence of confounding. Disadvantages are that long-term outcomes are not possible, the effect

can only be studies of one or two interventions and generalization is not always possible.

Mechanistic research studies the mode of actions and biological plausibility. In humans or animals this is called *in vivo*. *In vitro* covers research outside the organism, for example cells in a culture (Twisk, 2010). Benefits of this method are the controlled circumstances and it can be complementary to observational or RCT research. However, the extrapolation to the living organism can be insecure.

Figure 1 shows the different elements from which the human body is composed.

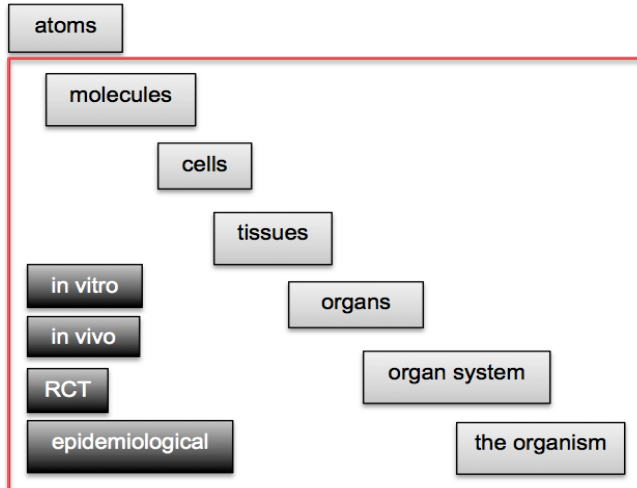


Figure 1: The structure of the human body, from small to large objects. In red lining the subjects studies by BMS and the possible methods to study them.

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The combined oral contraceptive pill and the increasing prevalence of inflammatory diseases in Western societies.

Anne Rotteveel - Biomedical sciences

Key points

- The pill suppresses and influences natural estradiol and progesterone levels within the female fertility cycle with synthetic compounds.
- The pill can induce many adverse effects, metabolically as well as symptomatically.
- The pill affects the immune system through changing the homeostatic situation and increases risk of inflammatory disease, such as cardiovascular disease and cancer.
- The pill has some non-contraceptive health benefits.
- Although effects of the pill differ in their magnitude health risk, the pill has to be used very carefully and women need to be well informed and monitored.
- The risk-to-benefit ratio of the pill has improved over years, newer pills are less harmful.
- Effects of long-term use on all aspects are not well known yet.

In this section, we studied have the effects of the hormonal birth control pill on the female body. First the mechanism of female fertility is described, followed by the mode of action of the combined oral contraceptive (COC). Thereafter the development of the COC is described. Next the positive and negative effects of the COC on physical health are assessed. Subsequently, we examined whether COC increases the risk of inflammatory disease, such as cancer and cardiovascular disease. This section is completed by looking ahead at how these insights relate to the final answer to our main research question.

Methods

The BMS approach was used to address consequences of continuous use of hormone-based oral contraceptives. The aim of this project was to determine whether the increased occurrence of inflammatory diseases such as cancer and cardiovascular disease can be attributed to the use of combined oral contraceptives.

A literature search was done, using publications found through online search engines such as PubMed and Google Scholar. Key search terms included: oral estrogen and progestin (also estradiol and progesterone), combined oral contraceptive (COC), oral contraceptives pathophysiology, inflammation, inflammatory disease, cancer and cardiovascular disease and hormone metabolism.

Subsequently, limitations were specified. Since we noticed that most side effects originate from inflammation we chose to focus on literature helping us explaining how COC use induces inflammation. Because little research is conducted in this field, we chose to use cancer and heart disease, since they are the most common examples of COC use related diseases. Many papers focused on (pre- and post-) menopause or specific side effects, which were not included in this literature research because they did not fit within the scope of this study.

Combined hormonal contraceptives are supplied in different formulations, including progestin only pills (POP) and combined oral contraceptive pills, from now on referred to as COC. In this project, we focused on the latter because it is most widely used (Hatcher & Nelson, 2004). COC exists in mono- and multiphasic forms; we chose to view them as one and the same.

Most journals from which papers in this study were used have a 5-year Impact Factor (IF) between 1.290 and 4.860. This is over five years the average number of citations received per year by papers published in the journal (Thomson Reuters, 2014).

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Glossary of terms:

At first it is useful to examine this glossary of terms, in order to understand the following text.

The reader can also check this list while reading.

Term	Explanation
Analogue	A compound that resembles another in structure (and can simulate its function). It is often used to block biochemical reactions.
Carcinogenesis	The emergence and growth of cancer
Carcinogens	Agents that stimulate cancer development
Chemokines	Subfamily of cytokines that influences the accumulation of cells.
Contraindication	This means that it can have negative side effects, or can interfere with other medicines, lifestyle habits or predisposed risk
Cytokine (+receptor):	Imagine it as a small ball, encounters the receptor, imagine this as a block, with a bite out, exactly in the form of the small ball. The small ball attaches to the block, and thus it is activated
Egg motility	The follicle/egg moves through the ovaries and the uterus in order to get fertilized by a sperm cell. When this motility is interfered, this decreases the potential for a sperm cell to reach the egg
Endometrium	The endometrium is the lining of the uterus. A fertilized egg implants in here, from which points it starts to develop itself and grows, to become a fetus, a baby
Feedback system	A feedback system, negative or positive, implies that two or more compounds keep each other's levels in balance
Follicle	A spherical structure within the ovary that contains an egg (oocyte).
Malignant	Or viciously: the tendency of a tumor to become progressively worse
Pathogenesis/pathogen	This means that it has the ability to induce disease
Pro-inflammatory	Induces inflammatory reaction
Tumor	Unregulated growth of cells, which can accumulate. This can be malignant (cancer) or benign.

Diseases:

Atherosclerosis	Calcification of the arteries. It is a major inducer of heart attack, infarction and brain bleeding.
Ischemic disease	A variety of diseases of the heart, caused by decreased oxygen supply (and thus reduced blood supply) to the muscle of the heart.

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Myocardinfarct	Also known as heart attack. The death of a part of the heart muscle as a result of an interruption of its blood supply by blood vessels. A heart attack occurs generally because a blood clot of an atherosclerotic plaque releases and blocks the vessel.
Pulmonary embolism	A blood clot in the lung, which can cause obstruction of the blood circulation, this can be very dangerous
Sepsis	Normally the blood is sterile; this means there are no bacteria in. Bacteria enter the blood, this can cause blood-poisoning, called sepsis.

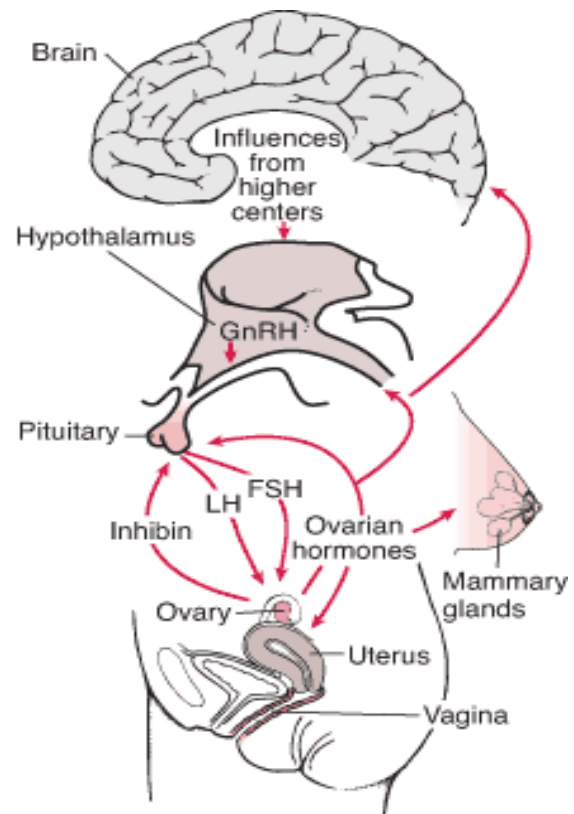
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1. Introduction and overview

Mechanism of fertility

The follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) are gonadotropin protein hormones (Gn). Gn hormones are essential for the regulation of growth, sexual development and the reproductive function (Johnson & Everitt, 2000, Ch. 6). They are secreted by the anterior pituitary gland in the brain. The hormones that induce the release of Gn's are called gonadotropin-releasing hormones (GnRH). In the gonads (ovaries), LH stimulates testosterone (T) production and thus indirectly estradiol (E2), as the latter is naturally synthesized from testosterone. FSH stimulates the growth and maturation of the follicles in the ovaries, it also incites follicles to produce estradiol (Stockhell & Renwick, 1992).

The hypothalamus can be seen as the control center of fertility in the brain and



maintains E2 and T levels at set values. This is a negative feedback system. When the steroid (sex hormone) levels exceed optimal values, the hypothalamus inhibits GnRH secretion, decreasing LH and FSH secretion by the anterior pituitary. An exception occurs when the negative feedback loop becomes positive. At high estradiol levels during menstrual cycle, LH and FSH secretion increases. This results in the ovaries releasing an egg (the ovulation). (Johnson & Everitt, 2000, Ch.15). The mechanism described is called the hypothalamic-pituitary-gonadal (HPG) axis, the fertility axis, which is visualized in *figure 2*.

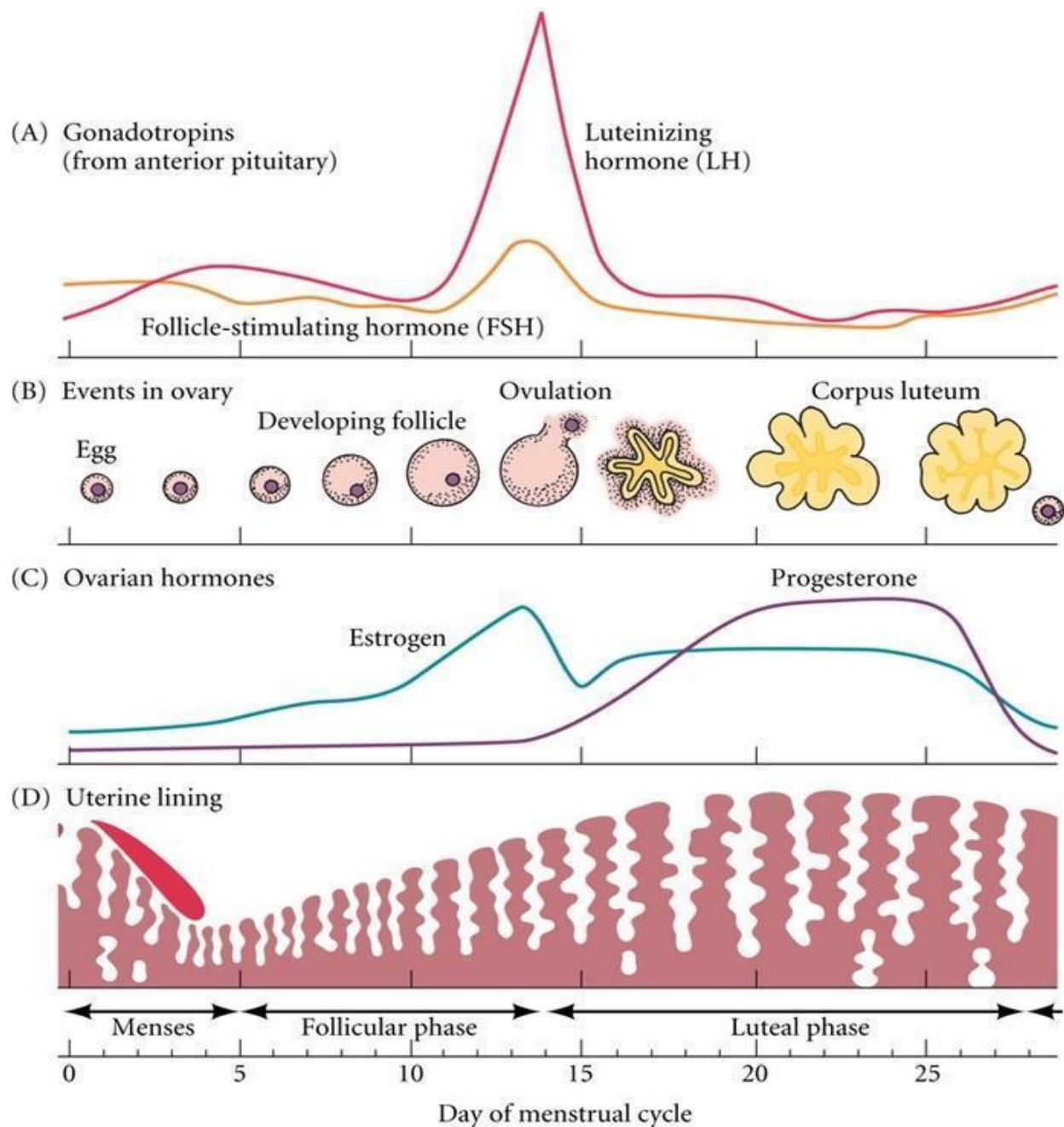
Female fertility follows a cyclic pattern, which is called the menstrual cycle.

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The menstrual cycle can be divided into two phases, the follicular/proliferation phase and the luteal/secretional phase (Johnson & Everitt, 2000, Ch. 15). These phases can be described on basis of changes in the ovary, the uterus and the production and secretion of hormones. Generally a human reproductive menstrual cycle lasts 28 days, ovulation

occurs at 14 days (see figure 3). In the follicular phase estradiol levels rise around day 12 as a result of LH and FSH dependent

folliculogenesis. When estradiol levels reach a specific set point, a LH surge release occurs which causes ovulation (3c). After ovulation, the remaining follicle starts to produce progesterone and becomes the corpus luteum. During the following luteal phase progesterone and estradiol levels remain high and FSH and LH levels are low.

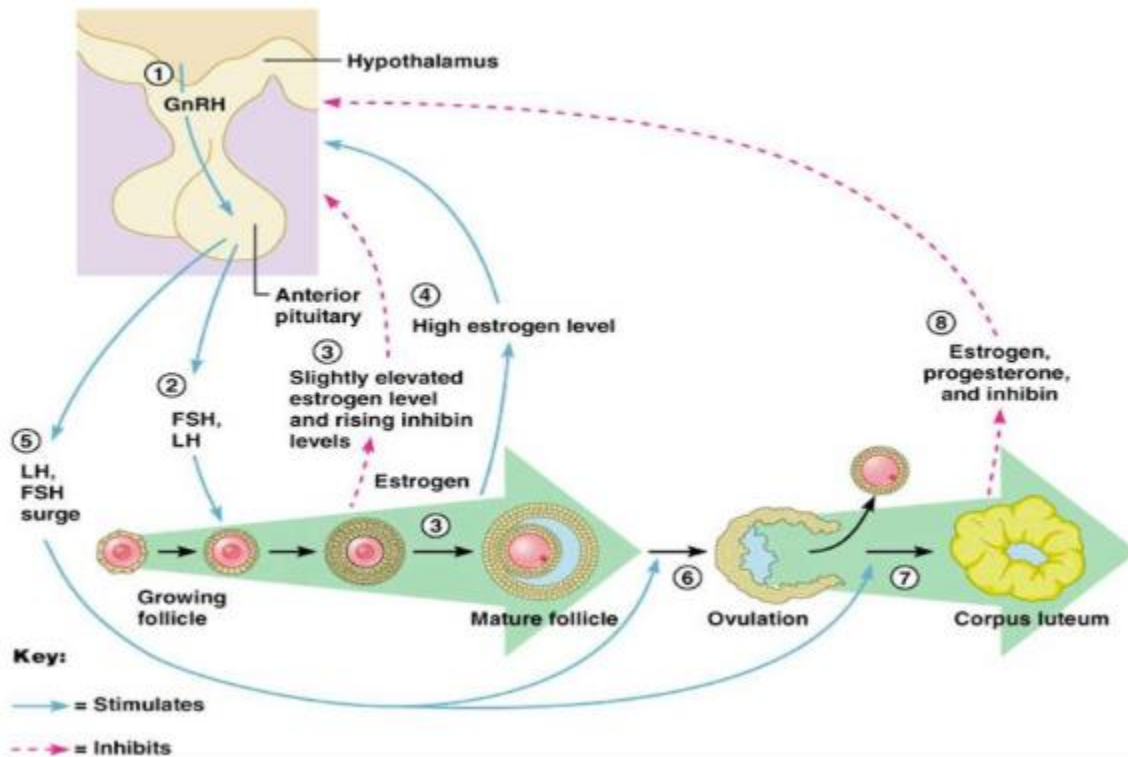


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At the end of the luteal phase the corpus luteum dies, progesterone and estradiol levels drop and FSH and LH levels rise to support folliculogenesis, after which menstruation bleeding occurs.

Figure 4 visualizes the influence of HPG-axis on the development of an egg.

The HPG axis hormones also influence the normal structure and



Subsequently, the cycle starts again.

functioning of the brain (Meethal & Atwood. Figure 4: The hormones that influence folliculogenesis. (Austin Community College, 2008) chapter (*Effects on Brain, Thinking and Behavior*).

Mechanism of combined oral contraceptives

The COC contains two major effective steroidal substances: estrogens (synthetic estradiol) and progestogens (synthetic version of progesterone). The general principle of mode of action of COC is the suppression of ovulation by the negative

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feedback effects of progesterone on HPG-axis. Progestin also has direct antifertility effects on the female vaginal sheath (genital tractus) to suppress sperm penetration by decreasing the water content and increasing viscosity of the cervix. It also negatively affects the receptivity of the endometrium. Estrogens support negative feedback, but mainly influence the tractus (Johnson & Everitt, 2000, Ch.15).

COC aims to prevent ovulation by inhibiting gonadotropin (Gn) release by negative feedback. Subsequently, FSH and LH secretion decreases. Thus no pre-ovulatory follicles are developed and no LH surges occur. Progestin negative feedback decreases GnRH release. Subsequently, FSH and LH secretion decreases. Low FSH levels inhibit follicular development and as such inhibit the increase of estradiol levels.

The absence of positive feedback by estradiol and the present negative feedback by progestin inhibits LH secretion and thus a surge. Both the inhibition of follicular development and the lack of a LH surge prevent ovulation (Nelson & Cwiak, 2011).

COC might induce endometrial swelling, which may negatively affect implantation and decrease of egg motility may interfere fertilization. However, long-term impact of these side effects on fertility during and after COC-use is less known (Nelson & Cwiak, 2011).

Although progestin is predominantly responsible for the contraceptive effects of COC's, estrogen remains an important component because its inclusion increases contraceptive efficacy and helps regulate bleeding (Blitzer & Simon, 2011).

2. Overview of the phases in development of the combined oral contraceptives

Generations

The first generation of contraceptive pills were developed in the United States in the 1960s, and contained high levels of synthetic estrogen with no progestin component. Since the addition of a synthetic progestin

was introduced, COC's can be categorized into generations according to the sort of progestogen that was added.¹ See figure 5.

In the first three generations of progestogens were derived from 19-nortestosterone (a form of testosterone) that caused androgenic side effects, which will be

¹ This classification is not science-based and not standardized, thus may differ between institutions and publications.

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referred to later. High doses of norethynodrel, norethindrone, norethindrone

acetate and ethynodiol diacetate were used as progestins in first-generation pills. These compounds had low potency and relatively short half-lives.

In 1956 it was demonstrated that the first contraceptive was contaminated with the estrogen mestranol (4-7%), an intermediate in the synthesis of the synthetic estrogen norethynodrel. The pill was purified to lower mestranol concentrations (1%). With these estrogen levels, in combination with low potency and short half-life of progestin, females started to suffer from unscheduled spotting and breakthrough bleeding. It was decided to compose a pill containing 2,2% mestranol, in combination with norethynodrel, called

Enovid (White & Marks, 2002). In 1957 it was discovered that the estrogen concentration in Enovid could be decreased

Figure 5: this table shows the variety of progestogens in order of their development; this leads to the division in generations. by 33%, without losing efficacy (Junod & Marks, 2002),

This decreased the prevalence of gastrointestinal side effects, without significant increase of bleedings. Soon after mestranol was introduced, ethinyl estradiol (EE) was developed. Currently, a newer form of estrogen is estradiol valerate (E2V). Also estetrol (E4) and estradiol are used (E2) (Sitruk-Ware & Nath, 2013). These new forms induce less change in hemostatic and metabolism parameters compared to EE-based oral contraceptives. However, they are still being further developed and not yet used frequently.

To eliminate the existing side effects, second-generation progestogens were developed to be more potent and prolonged half-lives than the earlier progestins (norgestrol and levonorgestrel).

	<u>1st</u>	<u>2nd</u>	<u>3th</u>	<u>4th</u>	<u>new</u>
<u>progestogen</u>	norethynodrel, norethindrone, norethindrone acetate, ethynodiol diacetate	norgestrol, levonorgestrel	desogestrel, norgestimate, gestodene	drospirenone, cyprosterone acetate	dienogest, nomegestrol acetate

These second-generation progestogens however, caused androgenic side effects. We will refer to this later.

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To sustain the positive progestin activity and simultaneously reduce the androgen side effects, which at the same time allowed increased expression of estrogen function, third-generation progestins were introduced in the 1990s: desogestrel, norgestimate and gestodene. The increased estrogen levels in these pills could attribute to an increased risk of venous thromboembolism (VTE). Studies were necessary before this pill could be launched in the EU.

In the fourth generation drospirenone is used as progestin. Drospirenone has an anti-androgenic profile. This property led to new, non-contraceptive applications of the COC. For example; treatment of acne and menstrual disorders (Nelson, 2011). Currently two pills exist possessing non-androgenic functions. Cyproterone acetate is a progestin compound in the pill that inhibits the androgen (testosterone) receptor. This can reduce acne symptoms over time. Especially the two pills this progestin is used in (the Yasmin and Diane-35) induce increased risk of venous thromboembolism.

Current situation

Currently the second-generation progestin levonorgestrel, predominantly in combination with 30 µg ethinyl estradiol, is the most used

COC, because it has the least side-effects. (Blitzer, 2011)

Latest developed progestogens are hybrids; this means that they possess a variety of the positive properties of previous generations. Dienogest (US) and nomegestrol (EU) have more thorough and various effects on the endometrium ² than prior generation progestins (Nelson, 2011). Products containing nesterone and trimegestone are still being developed. (Blitzer, 2011)

Currently development of the COC is focused at improving its function and reducing the risks. New progestins are invented. Genetic and protein-targeted methods are under investigation (Burkman, Bell & Serfaty, 2011). New birth control methods are being developed, such as a pill and an injection for men, and a vaccine for women (Samra et al., 2014). For example more targeted contraception may be possible by making impregnation of the egg by a sperm impossible. In such case the ovary function remains normal, as well as the estradiol and progesterone levels. *Figure 6* shows more specific potential targets for improving COC and inventing better methods.

Any statement in this text on the altered condition of COC users is always in contrast with average performance by naturally cycling (NC) women, unless stated otherwise.

² This means that they make it harder for the egg to implant in the endometrium in the uterus.

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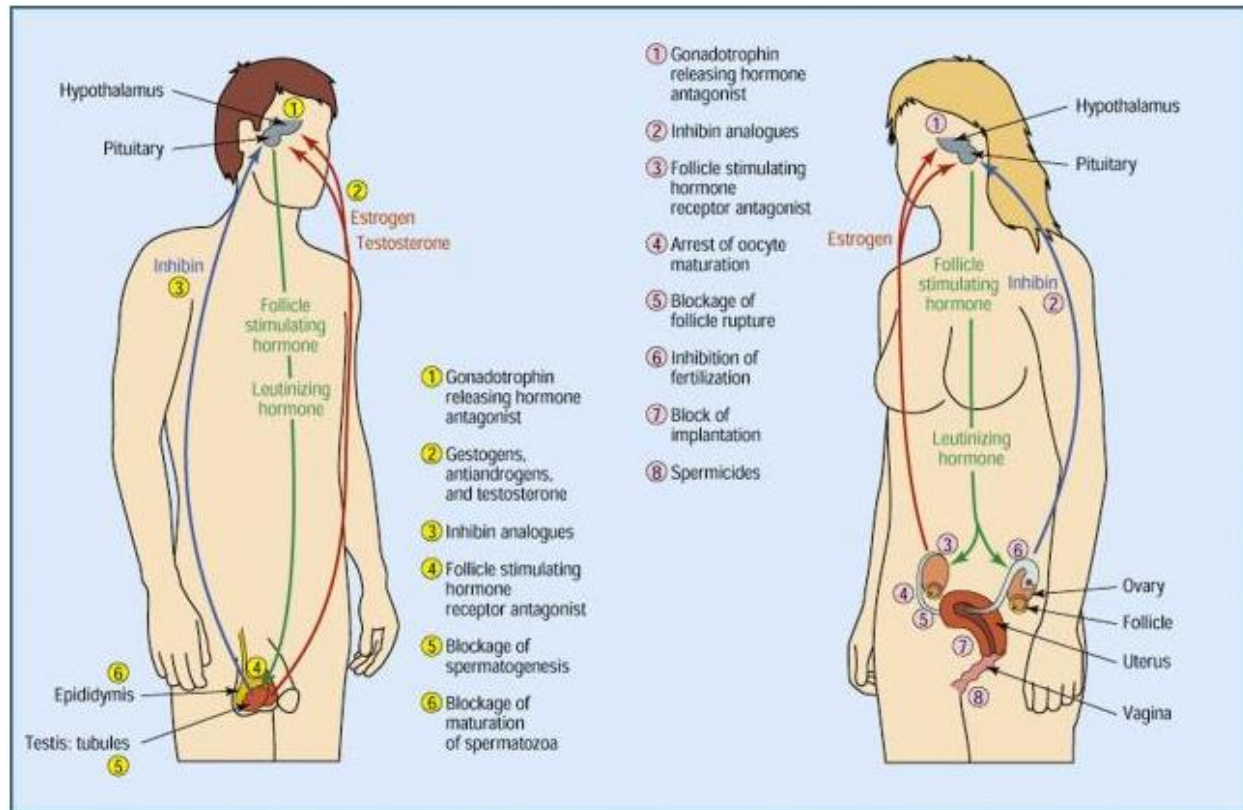


Figure 6: long term possible approaches for contraception in men and women (Baird & Glasier, 2000).

3. What are COC side effects?

Non-contraceptive health effects

COC use may have a positive effect against acne, ectopic pregnancy, bone thinning, non-cancerous breast growths, endometrial and ovarian cancer and anemia. It also benefits the menstrual cycle by reducing severe menstrual cramps and stabilization of the menstrual pattern (Sabatini, 2011). The negative effects of continuous COC use outweigh the positive non-contraceptive health effects (Maia & Casoy, 2008). For this

reason this paper will focus at the negative side effects.

Physical side effects

As with every medication, COC use has contraindications. Despite a highly rated safety profile of current COC's (Mansour, 2010), there is a risk of adverse metabolic, vascular and tumor-inducing effects. No combined hormonal contraceptive is absolutely safe (Bitzer & Simon, 2011).

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To prevent adverse side-effects by COC-use, it is important to inform patients about the possible side effects and perhaps to monitor them accurately during use. However, the latter is rarely done. It is important to tune contraceptive use on women's risk profile, familiar history (Sabatini, Cagiano & Rabe 2011), age, concomitant medications and preferences (Bitzer & Simon, 2011).

A randomized control study showed that women using the pill suffer from weight gain, nausea, headache (menstrual migraine), breast tenderness, irritability, depression and vaginal dryness (Sabatini et al., 2006). Progestins may affect metabolism, and have been implicated in increased risk of cardiovascular complications associated with COC's (Meade, et al., 1980, Sitruk-Ware & Nath, 2013, Lawrie et al., 2011). Also pulmonary embolism is a possible side effect (Parkin et al., 2011). COC use also increases risk at several cancers.

Because long-term effects of COC use have not been well studied yet, in this paper we focus on an underlying mechanism of the development of cardiovascular disease (CVD) and cancer. This will be explained in the following paragraph.

Androgenic effects:

Androgenic progestins in the first generations of COC are associated with symptomatic and metabolic effects. The symptomatic effects consist of unwanted,

male-pattern hair growth, hair loss, weight gain and acne. Newer contraceptive formulations contain less androgenic progestins or anti-androgenic progestins. Thus the androgen-related effects have been reduced (Jones, 1995). Glucose tolerance for example is a metabolic effect (Darney, 1995). In a later phase, anti-androgenic progestins were developed. COC containing these progestins do not show significant weight gain and do not show hair problems (Schramm & Steffens, 2002). Most of the adverse effects that come with the use of anti-androgenic progestins are non-specific or to be expected with COC-use in general (Raudrant & Rabe, 2003).

Consideration of risks and benefits

As regards to estrogen dose in COC, it is important to securely define this, to balance between the health risk of estrogen (referred to in the subsequent paragraph) and the better safety and tolerability (Alsina, 2010). Cardiovascular complications are the most severe side effects of COC use. In 1995 the risk was estimated at 21 cases per 100.000 users a year (Poulter et al., 1995). Despite this low absolute risk, women using COC have three to six times higher risk of venous thromboembolism, compared to women who do not use COC. This implies a risk at developing venous thromboembolism of 5-12 women out of 10.000 using COC, compared to 2 out of 10.000 women who do

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not use COC (Chasan-Taber, Stampfer, 1998, de Bastos et al., 2014,). The overall risk increases with age (Poulter et al., 1995). Women taking 3rd-generation pills have a 1,7 increases risk of venous thrombosis compared to those taking 2nd-generation pills (Kemmeren, Algra & Grobbee, 2001).

A meta-analysis in 2012 found a non-significant increase in the risk in breast cancer with ever OC use. There was a limited number of studies about long-term COC use, though these showed a significant greater risk at breast cancer (Zhu et al., 2012). COC use was also associated with a significant increase in the risk of cervical cancer. 5 or more years COC use increases the risk of cervical cancer with a factor of 1,9, compared to non-users (Appleby et al., 2007).

Contraception and menopause are related to the ovaries and their functioning, as do certain diseases. However the mechanisms of this relation require further research. It is known that disfunctioning ovaries, after menopause, highly influence women's health. In addition, people are becoming older than previously. On average, women spend a third of their lives after menopause (Broekmans et al., 2009). The question remains whether there is a relationship between continuous COC use

during fertile life and possible health problems, which occur after menopause. However, the causal relation of these occurring health problems remains elusive and needs further research.

In general, with the current knowledge, most scientists conclude that the benefits outweigh the risks of COC use. However, it is essential to this effect that women use it right. Compliance and continuation rates are generally overestimated. Many women stop using COC because of the side effects and/or fear of them. It is a prerequisite that women are being well informed, based on facts (Brynhildsen, 2014). Otherwise the positive effects of COC-use do not apply. For example, efficiency can be lost, and the prevention of unwanted pregnancy is not covered.

Despite this observation we discuss the basal mechanisms of the development of CVD and cancer and the indirect role of COC in it, in the following paragraph. Because it is of value to understand how COC use contributes to a certain extend to the increased prevalence of CVD and cancer in western societies. It predominantly provides insight for understanding long-term effects and a basis for further research.

4. What is the role of combined oral contraceptive use in the prevalence of inflammatory disease in Western societies?

Inflammation

A relation that might explain the detrimental side effects of COC-use is that they originate from an inflammation process. Inflammation is the body's immune-system's attempt to self-protection. It aims to remove dangerous stimuli, including pathogens and damaged cells, and to initiate recovery. Inflammation does not implicate an infection. Bacteria, viruses or fungi cause an infection, while inflammation is the body's response to it. Initially, inflammation is advantageous as it kills aberrant cells and potentially dangerous organisms. However, in some people it can cause a state of continuous inflammation, turning into a beneficial process.

There are two forms of inflammation, acute and chronic (long-term)(Serham & Ward, 2010). Chronic inflammation over time might cause diseases such as certain types of cancer, heart disease (i.e. atherosclerosis), periodontitis, rheumatism and several allergies. In this section we focus on diseases as a result of chronic inflammation. Autoimmune disorders are caused by misguided immune responses to healthy tissue, setting off an inflammatory response. In the following section,

cardiovascular disease (i.e. coronary artery plaque) and cancer risk as a result of COC use are studied, as important examples of chronic inflammatory disease (Scott et al., 2004)

How is inflammation triggered?

Several processes maintain the immune system in a homeostatic condition. The immune system functions as a balance. The first step consists of the T-Helper 1 System, the immediate immune system, which reacts against foreign invaders like bacteria. In this TH-1 system macrophages, natural killer cells and cytotoxic T cells are involved. In case the invader is not removed immediately, B cells from the TH-2 system will produce antibodies, which attach to the invaders, facilitating the TH-1 system. Messenger proteins such as cytokines, which are inflammatory, regulate the communication and coordination between the immune cells of the two systems. This shows that inflammation is a defensive reaction of the body to protect itself. It results in an increased blood flow in response to infection or chronic conditions, in order to 'solve the problem'. Any compound or process that

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increases cytokine levels, induces inflammation (Martini, 2008).

The hypothalamic-pituitary-gonadal (HPG) axis and the immune system:

Sex steroids engage on peripheral immune cells and primary lymphoid tissue. Lymphoid organs play a role in the regulation of immune response. (Suenaga et al., 1998).

Androgens and estrogens affect components of the immune system. Androgens may inhibit immune activity, whereas estrogen may stimulate immune activity (Verthelyi and Ahmed, 1994). GnRH and its receptors are expressed in immune cells (Silveira et al., 2002). This implicates that sex steroids and GnRH are important in modulation and development of the immune system, acting via the HPG axis (Mann et al., 1994). Most studies in this field though are experimental and use animals. Further research is required to show the possible impact of synthetic sex steroids use and its risks and benefits and to elucidate mechanisms in humans. *Figure 4* visualizes the interaction between HPG axis and the immune system.

Combined oral contraceptives, cytokines and their role in inflammatory disease

Immune cells produce cytokines. A cytokine is a messenger protein that is a part of the immune response. Thus they are only

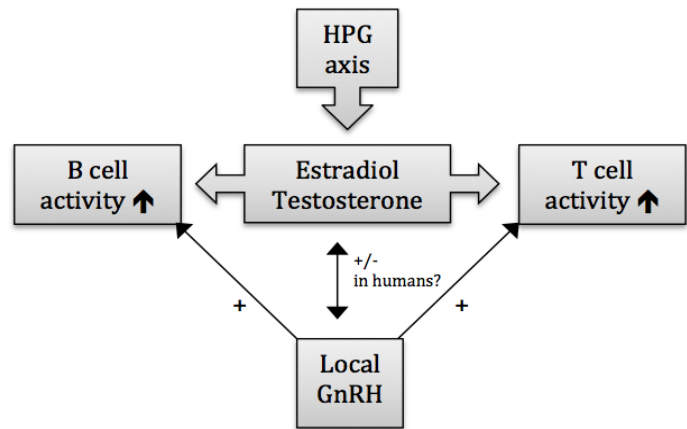


Figure 7: Representation of experimental data for interaction between immune system, sex steroids and GnRH. The HPG axis influences immune cell (B and T) activity through sex steroids. Local GnRH is produced by immune cells or – tissue and has a stimulatory effect on the immune cell activity. The interaction in humans has yet to be examined.

expressed during inflammatory processes and, when well-functioning, not in health. Many different forms exist. Cytokines are activated by cytokine receptors on immune cells. When these receptors encounter a pathogen, cytokines are produced. They regulate the balance in immune responses and influence their own release or of other cytokines. Cytokines are predominantly pro-inflammatory, but also anti-inflammatory cytokines exist (Dinarello, 2006). Cytokines can also inhibit each other. Cytokine interaction can lead to a cascade of processes (Arai et al., 1990). Generally, cytokine receptors are expressed for short period (Parham, 2009). When the immune system is unbalanced, inflammatory disease can follow. An underlying manifestation of this deregulation is the inappropriate

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activation of cytokines. This can lead to pathological effects (Dinarello, 2006).

It is recognized that estrogens can affect parts of the immune system (Olsen & Kovacs, 1996, Ahmed et al., 1999). In the normal menstrual cycle there's an estradiol surge (see *figure 2*), but this cycle is disturbed by the additional intake of estrogen from COC's. Exogenous estrogen intake from COC induces estradiol surges with which the body is not familiar. The body's immune system subsequently may respond to this. Estrogens in COC cause an increase of inflammation indicating agents (Kluft et al., 2002). Estrogen may mediate the effects on the immune system through regulation of cytokine release. Cytokine levels increase and induce inflammation. This may cause misbalance in the immune system. However, effects of sustained estrogen exposure on cytokines is not well known yet. Experimental research on mice confirms that estrogen can modulate certain cytokines (Karpuzoglu-Sahin et al, 2001, Gilmore, 1997). It could be genetic predisposition what kind of inflammatory reaction the incitement of the immune system will induce, and subsequently in what disease this will be expressed (Arai et al., 1990).

Cytokines and cancer

Cancer is a process of abnormal cell growth, which can become malignant and can potentially spread to other parts of the body

(WHO, 2010). Imbalances of inflammation, estrogens and progestogens play a role in the development of cancer. A pro-inflammatory situation can increase estrogen production. Increased levels of estrogens, as a result of COC use, may result in development of the endometrial tissue into tissue that grows uncontrolled. The fact that chronic inflammation can induce rapid cell division, enhances this effect. On the other hand, progestogens (in COC), decrease inflammation. (Modugno et al., 2005). As a result of sustained COC use the risk of endometrial and ovarian cancer appears to be reduced, whereas the risk of breast, cervical and liver cancer appear to increase (Burkman, Schlesselman & Zieman 2004). This shows a remarkable paradox in the influence of cytokines on cancer development (Dinarello, 2006, Straub, 2007). See *figure 8*.

Using cytokines to fight a tumor may be a promising therapeutic approach for cancer therapy (Golumbek et al., 1991). In therapeutically applications, substantial

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inhibition of cytokines reduces further tumor development, but it does not destroy tumor cells, nor prevent carcinogenesis. This supports the outcomes that pro-inflammatory cytokines increase the development and growth of a tumor (Dinarello, 2006). In chronic inflammation, the persistence of pro-

tumor development. From that moment on, immune suppression starts, which in addition has negative effects (Song et al., 2005). A combination of estrogen with certain cytokines has a stronger effect on breast cancer cells than each of the elements alone, appeared in a experimental study. Cytokines

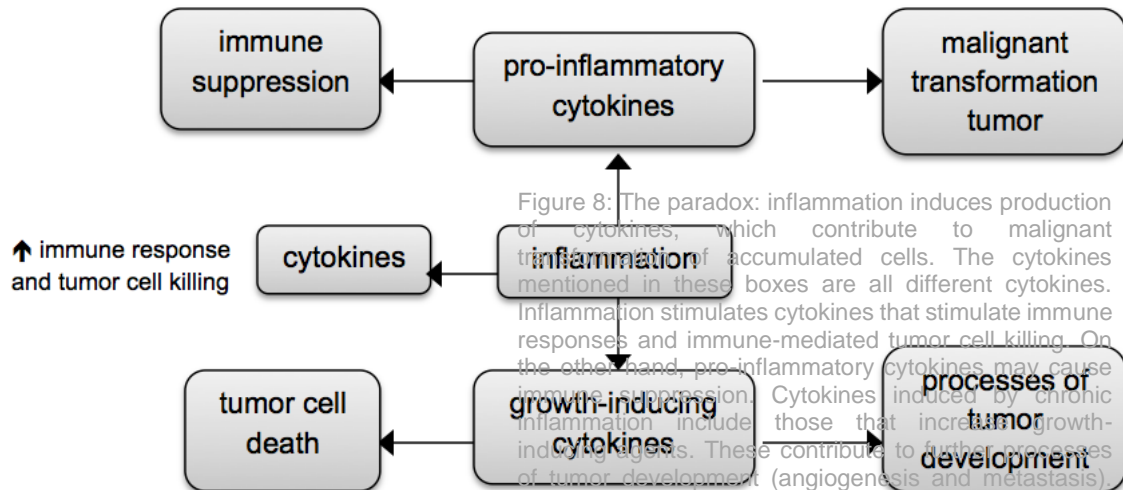


Figure 8: The paradox: inflammation induces production of cytokines, which contribute to malignant transformation of accumulated cells. The cytokines mentioned in these boxes are all different cytokines. Inflammation stimulates cytokines that stimulate immune responses and immune-mediated tumor cell killing. On the other hand, pro-inflammatory cytokines may cause immune suppression. Cytokines induced by chronic inflammation include those that increase growth-inducing agents. These contribute to further processes of tumor development (angiogenesis and metastasis). However, these same cytokines may also indirectly induce direct tumor cell death (based on: Dinarello, 2006, Straub, 2007)

inflammatory cytokines maintains the chronic inflammation and thus causes cancer (Colombo and Mantovani, 2005).

Chronic inflammation and its concomitant cytokine production is an important mechanism in carcinogenesis (Balkwill et al., 2005). In the absence of pro-inflammatory cytokines, carcinogens are unable to induce malignant transformation of tumors (Borello et al., 2005). Cytokines can function as tumor growth inhibitors as well as tumor growth stimulators (Tartour and Fridman, 1998). In early stages of inflammation, the effects of cytokines on the immune response are beneficial, however they may become overruled by increasing

can turn into strong cancer enhancing factors in combination with estrogen (Weitzezenfeld et al., 2013).

Cytokines and cardiovascular disease

Cardiovascular disease (CVD) comprises diseases that involve the heart, the blood vessels or both. Acute coronary syndrome, stroke and venous thromboembolism form the top-3 of CVD. (Goldhaber and Elliot, 2003). But also high blood pressure (hypertension), ischemic heart disease, acute myocardial infarction are common cardiovascular problems. Atherosclerosis is

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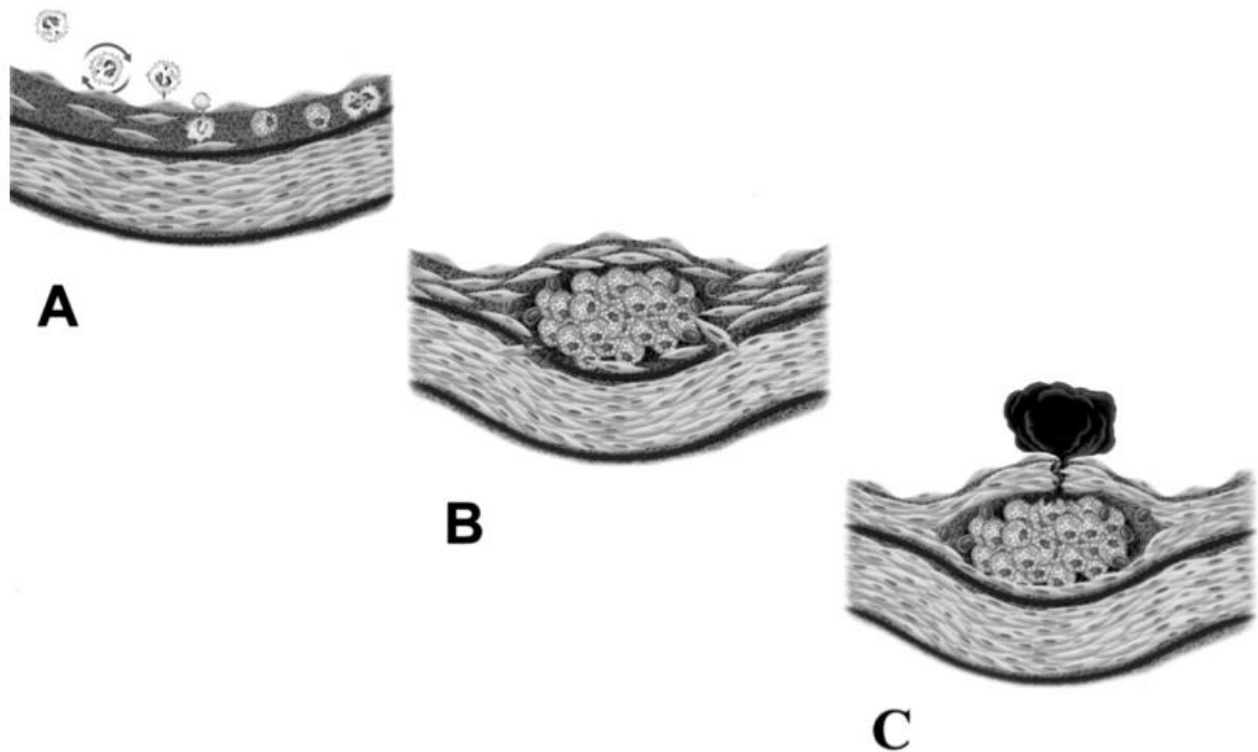
considered to be the major precursor in CVD. Atherosclerosis starts with the activation of the wall of the blood vessel (the endothelium). This makes it more receptive for cytokines. (Pro-inflammatory) cytokines have a complex and essential role in the development of atherosclerosis. The cytokines can alter the function of the endothelium, which may result in a loss of barrier function, altering the distribution of nutrients and promotion of recruitment of cells that in will form the plaque. These implications accelerate the process of plaque formation (Weber, Zemecke & Libby, 2008, Kleinbongard, Heusch & Schulz, 2010). Subsequently several processes, involving cytokines, lead to the formation of a plaque, a layer of accumulated cells covering a small part of the endothelium. When certain cytokines are in a layer of the endothelium, they become activated by local cytokines, which also induces plaque-promoting processes. The compounds that have properties to inhibit plaque formation, are also altered by cytokines, which proves the plaque formation more latitude (Esmon, 2004).

When this plaque continues to grow it can form an occlusion of the blood vessel, which can result in ischemic disease. The plaque can also 'explode' (it ruptures), releasing a blood clot (thrombus) in the vessel. This occurs because in an advanced stage of atherosclerosis, pro-inflammatory

cytokines destabilize the plaque, magnifying it and thinning the remaining protective cap (Clarke et al., 2006). The released clot may get stuck in a small (part of the) vessel, with subsequent cardiovascular disease consequences, for example a stroke (Tegos, 2001, Libby, 2006). The inflammatory cascade process is visualized in *figure 6*.

Cytokines can directly and indirectly influence the heart function, a hypothesis that is based on the observation that overexpression of pro-inflammatory cytokines mediate most aspects of a failing heart function (Seta et al., 1996). Elevated levels of pro-inflammatory cytokines are associated with CVD risk, independent of other risk factors. A slight increase of the basal cytokine level is associated with 10-25% greater risk at non-fatal myocardinfarct or CVD mortality. These associations may even be greater. However, more evidence is needed to state a causal role for cytokines in

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CVD (Libby, 2007, Ridker, 2014). Estrogens and progesterones have shown significant, though opposite effects in inducing vascular inflammation. Estrogens may have an anti-inflammatory effect on blood vessels, whereas progesterones oppose this positive effect, exacerbating the inflammatory response (Sunday et al., 2006). Progesterones may exacerbate inflammatory response in blood vessels. Progesterone in combination with estrogen, partially negates the beneficial effects of estrogen on cardiovascular functioning. However, studies conflict, some find beneficial effects (Simoncini et al., 2004) of progesterone, some no to little effect (Simoncini et al., 2003), and some a negative effect (Sunday et al., 2006).

Figure 6: participation of inflammation in all stages of atherosclerosis. When the endothelium becomes inflamed, cytokines can easily attach to it. Pro-inflammatory cytokines attract other cytokines to migrate to the endothelium and accumulate. Subsequently T cells join the accumulation and start secreting cytokines that weakens the structure of the vessel. The plaque is formed. When the plaque ruptures, a blood clot is released (Libby, Ridker & Maseri, 2002).

5. Final Remarks

The purpose of this section of the study was to answer the question to what extent COC use contributes to the increased prevalence of inflammatory disease in western societies. Inflammatory disease such as CVD and cancer are the leading cause of death in western countries. The insights imply that inflammation as a result of COC use does contribute to increased risk of CVD and cancer, however, only to a very small extent and as such constitutes only one of the many factors that induce these pathological problems. We thoroughly studied the influence of COC on the inflammatory processes that underlie CVD and cancer. Combining these results with epidemiological results, COC use statistically does not form a significant predominant factor in the prevalence of CVD and cancer.

On the other hand, it needs to be taken into account, that many of the inflammatory diseases mentioned develop at older age. The worldwide COC use is a long-term research on the effects itself. However, with the start of the distribution in the 60's, assuming that the youngest users would be 20 when starting to use the pill, these women at most have reached the age of 70. Assuming that, there is not yet a large group of women of older age, from whom effects

can be measured. And further research is required a more and profound relations, such as mentioned in this section need to be studied.

Opinions differ, and many women are suspicious about the pill. To bypass hormonal influence of the female menstrual cycle, other, more targeted, contraceptive methods could be developed. This does require further research. The results thereby indicate that estrogens form the biggest problem in COC's. Arising from this, we may state that the progestin-only pill would be a preferable option for women as birth control. This would decrease the adverse side effects and would be beneficial to compliance and continuation of use.

The risk-benefit assessment showed that on statistical basis, risks of COC use do not outweigh the benefits. This would implicate that COC use may have had a neutral effect on the position of women in western societies, based on their physical conditions. However it is important that women are well informed, supported by facts, to prevent interruption or discontinuation of use. This may interfere with the positive societal effects of pill use since its introduction.

Chapter 3

Behavioral Neurosciences approach

Interdisciplinary remarks

The interdisciplinary field of behavioral neuroscientific research is defined by a core of methodological and epistemological assumptions that borrows heavily from one of its key constituent disciplines: Biology. The academic field of biology is essentially involved with the study of living organisms, seeking explanations for their functioning and behaviors by means of uncovering their biomechanical and biochemical constituencies (Repko, p.102). Through the analysis of empirically gathered data in either natural contexts or through experimental procedures, it attempts to infer causal relations between biomechanical processes and observed behaviors. The subfield of biology that is occupied with the study of humans continues on these principles, yet finds itself limited when attempting to explain the hugely complex phenomena of human behaviors. Although traditionally biology only uses objective, empirically gathered data to explain human behavior, the subjective phenomena surrounding the 'mind' might provide new insights to overcome its limits.

Psychology - the other key constituent of the interdisciplinary field of the behavioral neurosciences discussed here - is arguably home to a far greater variety of schools of thought than biology. This is hardly surprising considering its main area of research includes the intuitively graspable, yet elusive mental phenomena that make up human thinking. Whereas human behavior can be studied using the traditional methods of the natural sciences, mental phenomena are inherently subjective - only visible through the eyes of the beholder. Any scholar theorizing about these subjective experiences ultimately has only their own mind for reference, such that direct independent observation of these phenomena is essentially impossible. For behaviorists - who were motivated to eventually push psychology into the realm of the natural sciences - this was cause to reject the existence of subjective experiences altogether and stick to the study of

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observable behavior.³ Other schools choosing inclusion of the study of mental phenomena vary greatly in their epistemological assumptions, nearly all of them in some fundamental way conflicting with others. Contemporary psychological thought appears to shift increasingly toward the reductionist biological ideas about the causal origins of human thinking and behavior. Whereas some traditional - and still influential - schools of thought in the behavioral sciences continue to instill some notion of the irreducibility of mental phenomena, many modern psychology scholars are no longer adhering to this idea. This does not mean that every fruitful modern psychological approach to the study of human behavior is at once compatible with neuroscientific insights, as both cognitive and social psychology have long been producing well-functioning theories without explicit regard for neural systems. Per definition, these theories provide imperfect but sensible models of human thinking as is measured by their predictive values. It is at the crossing paths of progressive biology and psychology scholars who seek to investigate human thinking and behavior beyond the limits of their disciplinary boundaries, that we find the interdisciplinary field of the *behavioral neurosciences*.

³ Behaviorism can perhaps be considered closer

to biology than psychology, as its study of human behavior is nearly synonymous. With the focus of this study on the effects of the pill, the perspective of the behavioral neurosciences is made up of a number of assumptions, methods and techniques. First and foremost: human behavior is regarded as the result of, or even synonymous with the physical state of the brain's biochemical operation. These operations are determined by innate traits (genetics), and external inputs of both physical and non-physical nature. The biological approach is essentially physicalist, so the study of human behavior advances by finding the physical mechanisms that cause the non-physical (mental) phenomena that result from pill use.

Studying effects of the pill in various places in the physical chain of causality is done using a number of techniques. This chain of causality is pictured in the figure below, with a couple of general techniques of assessment placed on the right side of their domain of measurement. All studies of some aspect of the brain correlated with behavior are cross-modal, with functional neuroimaging most explicitly aimed at the uncovering the interface between neural activity and behavior. It should for the sake of simplicity here be considered to include some active manipulation experimental techniques (i.e. transcranial magnetic stimulation - TMS) as these provide similar

to biology than psychology, as its study of human behavior is nearly synonymous.

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insights in (cortical) neural systems, but are arguably just as crude in the inferences that are ultimately (academically) allowable.

In this specific case, the oral contraceptive pill is of a huge hormonal influence, so most - if not all - of its effects

are considered causes of behavior at the bottom of the chain - the Hormones. From there any effects on other aspects of the brain can be studied using different techniques, but all starts with 'the great hormonal experiment'.

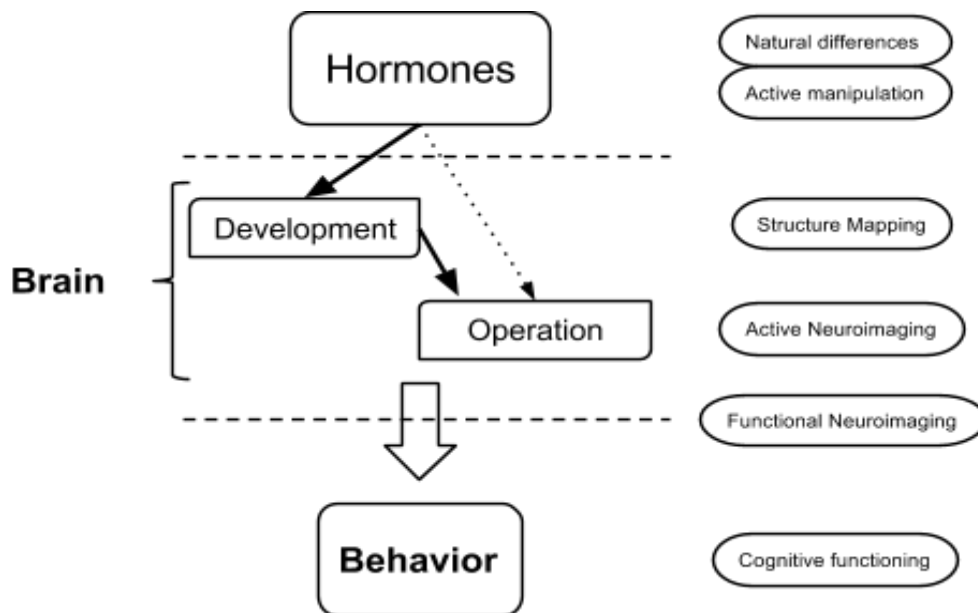


Figure 1

The greatest hormonal experiment ever?

How the combined oral contraceptive affects females' brains, thinking and behavior.

Duncan Huizinga - Behavioral neurosciences

Key points

- The menstrual cycle is both cause and effect of strong fluctuations in major sex hormone levels. The hormonal birth control pill largely suppresses the absolute levels of these hormones and their fluctuations across the menstrual cycle, and partially replaces them with synthetic hormones.
- The combined oral contraceptive (COC) pill is composed of synthetic derivatives of the two major sex-steroids estradiol (E2) and progesterone (P4).⁴ The most commonly used estrogenic component in previous and current generations is ethinylestradiol (EE). Synthetic progestogens in the COC vary, differing greatly in their 'masculinizing effects'.
- COC use is found to relate to differences in brain structure and functioning, affecting cognitive performance in memory, language and visuospatial processing.
- The COC can have a negative impact on mood and stress processing. Pill users show greater difficulty in unlearning fearful memory associations, and may be more strongly affected by stress.
- The COC can influence sexual preferences and mating behavior, most profoundly affecting women's behaviors when taking up or ceasing use while in a relation.
- Current knowledge on the COC's effects on brain and behavior is unstructured, scarce and in need of more research - especially regarding long term effects.

In this chapter, we investigate the effects of the hormonal birth control pill on the female brain, cognition and behavior. Using knowledge gathered from the biological, behavioral and the neurological sciences, we first discuss the effects of the COC on the neuroendocrine (hormonal) systems of the brain, and effects seen on brain development. We then consider the effects of the COC on cognitive performance and social behaviors, and link these to the current body of research on the influences on the biological mechanisms at the basis of these behaviors. It is the primary goal of this research to identify how the birth control pill affects its users; therefore, this research shall focus on some of the most clearly observed differences between users and non-users.

Methods

In order to gather information on the topics discussed here, a preliminary literature search was conducted using publications found through the Google Scholar and Web Of Science online search engines. Key search terms included: combined oral contraceptive, birth control pill, ethinyl estradiol, progesterone, cognition, social, behavior, neuro[*], endocrine, hormonal, or any combination/derivative of the aforementioned. This generated a limited number of applicable research articles, of which many that specifically dealt with medical pathological research were left out, as these were mostly not within the scope of the current investigation. Additionally, four very recently published (Q3 2014) reviews were found, that were closely related to the topic of this article (Pletzer & Kerschbaum, 2014; Gogos, Wu, Williams & Byrne, 2014; Toffoletto, Lanzenberger, Gingnell, Sundström-Poromaa & Comasco, 2014; Warren, Gurvich, Worsley & Kulkarni, 2014). These reviews cover a large part of the relevant literature up to the second half of 2014, and have therefore been used extensively in the search for further resources. The literature on the topic of this chapter is largely limited to the effects of the natural sex-hormones and chemicals in the COC on individual women. This explorative study will nonetheless attempt to identify some broader patterns than have been described in previous research, so must at times be more suggestive than would be considered best practice in the field of the behavioral neurosciences. The reader is asked to bear in mind that some of the conclusions drawn below require more extensive research. This will be elaborated upon in the conclusion.

1. Endocrinological underpinnings

The combined oral contraceptive (COC) pill is composed of an estrogenic and a progestogenic component⁵. Estrogens, in particular estradiol (E2), are the primary female sex-hormones (or sex-steroids) and are highly influential in the development of females' secondary sex characteristics. Progestogens, in particular progesterone (P4), are especially important during the menstrual cycle when women are most fertile. E2 is naturally produced in various ways, among which is its derivation from P4. It is also synthesized from the androgen testosterone (T), which is the primary male sex-hormone (and serves a similar role in development of males' secondary sex characteristics). E2 and P4 are both heavily involved in the menstrual cycle, bioavailability (blood levels) fluctuating strongly over its course (*for a more detailed description of the underlying biological processes, see the previous chapter by Anne Rotteveel*).

Contained in the COC are a synthetic derivative of E2 - ethinyl estradiol (EE) - and

one of a large variety of *progestins* (synthetic progestogens). E2 and EE are thought mostly identical in their biochemical workings - both primarily act by activation of the estrogen receptor - but EE has a specific molecular structure that greatly increases its potency as well as its half-life, which enhances its effects over time (i.e. it takes less to elicit similar effects and it remains bioactive in the blood for longer; Sitruk-Ware & Nath, 2013). The COCs progestin component takes various forms of which only the newer generations are derived from natural progesterone (P4). Progestogens primarily activate the progesterone receptor. Older generations of COC's generally contain a derivative of the androgen testosterone (T) and therefore also activate the androgen receptor, causing androgenic or 'masculinizing' side-effects⁶. Newer generations of progestins do not have such androgenic side-effects, as they only target the progesterone receptor (Sitruk-Ware, 2006). Intriguingly, as the COC suppresses females' endogenous T levels, irrespective of

⁵ Estrogens, progestogens and androgens are classes of sex-steroids. In females - among other things - the first two are important regulators of the menstrual cycle. Estrogens are well known for stimulating development of the female secondary sex characteristics, whereas this development in males is stimulated by androgens (i.e. testosterone). Both sexes produce estrogens and androgens, differing only in the levels that naturally occur in the body; stimulating one or the other can cause enhanced expression of associated secondary sexual characteristics, even in the opposite sex (i.e. raising/lowering the voice, bodily/facial hair growth, breasts/muscular growth).

⁶ Masculinizing and feminizing are in parentheses, as these are culturally laden terms. Here however, they signify objectively observable differences in brain, brain functioning and associated behaviors between the sexes. See previous footnote.

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the progestin component (Zimmermann et al., 2014), it is imaginable that - through the lack of androgenically active progestins - the newer generations of COCs even exert 'feminizing' effects on brain and behavior.⁷

While the interplay of the natural and synthetic sex-steroids in the brain is incredibly complex, it is well observed that the steroids contained in the COC profoundly affect the presence of many endogenous hormones. In naturally cycling (NC) women - not using any form of hormonal birth control - E2 and P4 levels are relatively low during the early-follicular phase (after menstruation, before ovulation) whereas in the mid-luteal phase (after ovulation, before menstruation) E2/P4 are relatively high.⁸ One of the first studies on the cognitive effects of the pill by Gordon and Lee (1993) reported that overall, COC users had strongly reduced blood plasma levels of natural estrogens and progestogens, averaging at around 50% lower compared to NC women. Similar or even greater differences were reported in other studies that conducted blood hormone assays (Islam, Sparkes, Roodenrys & Astheimer, 2008; Mordecai, Rubin & Maki, 2008; Graham & Milad, 2013) or analyzed saliva samples (Griksiene & Ruksensas, 2009; 2013).

⁷ This thought was put forward in a recent review by Pletzer and Kerschbaum (2014).

⁸ During menses sex-hormone levels are considered to be at their lowest, but this phase is

Changes in hormone levels and their associated human behaviors are known to occur as fast as minutes after environmental stimuli (i.e. physical stressors, social events), as well as after intake of various bioactive substances. When elicited through direct administration of sex-steroids, changes can last up to several hours and affect behaviors even for several days, depending on the hormone (Bos, Panksepp, Bluthé & Honk, 2012). Studies on the acute behavioral effects of estrogens and progestogens in women are scarce, but both are known to exert very rapid effects on the neural level (Balthazart & Ball, 2006; Pang, 2012).

In light of the aforementioned, any investigation into the effects of the COC on women is required to correct in some way for the various stages of the menstrual or contraceptive cycle, as well as for the androgenic property of the progestin. Although E2 and EE both primarily take effect by binding to the estrogen receptor, their exact similarities and differences in neurobiological and psychoactive effects are scarcely researched and remain unclear. It is for this reason that direct effects of the more potent EE cannot simply be inferred from knowledge about E2. The same goes for synthetic progestins and natural P4. The

almost never reported in the studies dealt with here, perhaps because of the relatively small time-frame available for assessment. (See Anne Rotteveel in this publication.)

latter shows an ambiguous interaction pattern with E2; in certain cases antagonizing its (neural) effects, in others enhancing or mimicking them (Baudry, Bi & Aguirre, 2013). The complexity of their study is further compounded by the great diversity of progestins. A few studies discussed below do find some striking short- and long-term effects on brain anatomy and activity in COC users, but observing differences and interpretation of associated behavioral patterns remains a difficult task so should be done with care.

Finally, because of the COCs profound impact on endogenous hormone levels, any effects cannot only be regarded as the result of the direct influence of its constituent

substances. Variations (and therefore also the suppression) of natural E2/P4 levels in itself are known to cause changes in brain and behavior, as is already apparent in women in the different stages of a single menstrual cycle (i.e. Farage, Osborn & MacLean, 2008; Weis et al., 2008; review: Toffoletto et al., 2014). For that reason, studies into the effects of natural estradiol and progesterone (i.e. the menstrual cycle) on women's brain and behavior are also discussed below.

Any statement in this text on the altered performance of COC users is always in contrast with average performance by naturally cycling (NC) women, unless stated otherwise.

2. Effects of the COC on cognitive performance

It is unanimously agreed among reviewers that the current body of research on the (neuro-)cognitive effects of the COC is still weak. Often remarked is the lack of a systematical approach and standardization of tests (Pletzer et al., 2014). Methodologies appear weak in many cases (Warren et al., 2014), and experimental research has mostly only focused on short-term effects (Toffoletto et al., 2014), whereas the pill is often used over the course of many years. Among other things, this leads one reviewer to conclude that “we generally know more about the

activation than organizational effects of sex hormones” (Little 2013), as observation of the latter appears limited by the small time-frames of the experiments. Nonetheless, a variety of significant effects have been observed (Gogos et al., 2014) which mandates further research.

Here we take a closer look at the cognitive domains of memory, verbal and visuospatial performance, as these appear to be most studied and promising. Additional attention is paid to how various levels of natural hormones exert a different or a

similar influence on cognition as compared to the synthetic hormones of the COC.

2.1 Memory

Some of the most profound cognitive effects of the COC on users are found in the memory domain. Memory in its broadest sense entails the absorption of information from, or provision of information to various other cognitive processes.⁹ In cognitive psychology, the concept of memory is further broken down into short-term (STM) and long-term memory (LTM). When performing an immediate recall task, performance is dependent on the ability to keep unprocessed information available in STM (see: Baddeley, 1992), whereas delayed recall requires long-term storage (learning, consolidation) and retrieval. The two brain areas that have long been known to play a central role in STM and LTM are the prefrontal cortex (PFC; D'Esposito, 2007) and the hippocampus and parahippocampal areas, respectively (Yonelias, 2002). Pletzer and colleagues (2010) performed brain scans (MRI) on COC users and reported larger gray matter masses (i.e. more brain cells) in both these prefrontal and the parahippocampal areas. This is suggestive

⁹ Nearly all cognitive processing places some demand on various aspects of memory, and it can therefore hardly be regarded as a separate domain. Nonetheless, memory as intended here is about the ability to retain or recall information about previously observed stimuli, and therefore not about any manipulations or subsequent

of increased STM/LTM capacity and processing at these sites compared to non-users.

With regard to STM performance, Griksiene and Ruksensas (2009) reported that COC users performed better on an immediate recall task using a visually presented digit span (7 to 9 digits). Variations in natural E2 levels in NC women did not predict performance differences. Gogos (2013) conducted a full range of neuropsychological tests¹⁰ on COC users that included memory tasks, among which were immediate recall of a visually presented word list (STM) and a read-aloud story (STM/LTM). Their findings showed COC users and NC mid-luteal (high E2/P4) women outperformed NC women during early-follicular (low E2/P4) phases, and men, on both tasks. Interestingly, here high natural E2/P4 appeared to enhance performance, suggesting the synthetic EE and progestagens in this case substituted for the lowered endogenous E2/P4 in pill users. The difference with results by Griksiene and Ruksensas (2009) may relate to this study using words and spoken language as opposed to a digit span in the former, the relevance of which is further discussed under

effects of the content. Memory is necessarily tied to the process of learning, so some research into effects of the COC and ovarian hormones on learning is also taken into consideration.

¹⁰ Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). See: www.rbans.com.

Verbal and Visuospatial Thinking.

In delayed recall tasks, testing for LTM, pill users generally show similarly affected performance. Mordecai, Rubin and Maki (2008) reported that women using the COC performed better when recalling a list of previously heard words after a 20 minute delay, with even better results on their active pill days compared to inactive days. Natural E2 levels did not predict performance. Gogos (2013) generated similar results in a comparable task, but tested only on active pill days. In this study, however, NC women in high E2/P4 phases performed on par with pill users. A study by Wharton and colleagues (2008) that tested for word recognition memory, showed no scoring differences between groups. However, recognition memory was tested after a 5 minute interval filled with multiplication tasks. The lack of differences is therefore likely explained by the multiplication task's load on STM, preventing rehearsal of the previously observed information and thereby hindering transfer to LTM in all participants (Baddeley, Eysenck & Anderson, 2009).

Results by Griksiene (2009), Gogos (2013) and Mordecai (2008) indicate that improved STM/LTM performance in pill users is not exclusively attributable to changes in endogenous E2 levels. This is evident as women who used COC (which lowers E2/P4)

consistently showed better memory than NC women low in E2 and/or P4. What remains unclear is whether and how the synthetic hormones from the pill replace natural hormones. To be more precise, it is unclear in what way the exogenous sex-steroids (EE, progestagens) in the COC functionally substitute¹¹ for the suppressed endogenous E2 and P4 levels. As E2 has been found to be important in the formation of long term memories in the hippocampus (Baudry, Bi & Aguirre, 2013; Frick, 2013), the findings by Gogos (2013) alone could reflect that such a functional substitution does indeed take place. However, there are no human cognitive performance studies that provide direct support for this line of thought. Furthermore, the only administration study on the differential effects of EE and E2 has been performed in rats, where EE was actually impaired and subsequent administration of E2 (re-)enabled recall of certain emotional memories (Graham & Milad, 2013; see [Negative Mood and Stress](#)). It is then arguably unlikely that in the neural mechanisms of memory (especially LTM) such a functional substitution of E2 by EE occurs.

An alternative explanation may be provided by the COC's suppressing effects on P4 levels. Administration studies on rats reveal that P4 negates some of the memory-

on behavior are similar.

¹¹ Functional substitution means that the effects

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enhancing effects of E2 (Bimone-Nelson, Francis, Umphlet & Granholm, 2006). Although suppression of the endogenous sex-hormones in COC users occurs in both circulating E2 and P4, it is not evident that these levels have a predictable 'linear' effect on associated brain activities and behaviors. In other words, the suppression of P4 could enhance memory performance more than it is deteriorated by the lowered E2. Such an explanation would be more consistent with results by Griksiene (2009) and Mordecai (2008). Their research did not account for variations in P4 levels, so endogenous E2 levels may not have significantly predicted performance because P4 balanced out its effects. This also fits with Gogos (2013), who reported that STM and LTM also improved in NC women in high E2/P4 phases of their MC. However, because this study included no direct assessment of hormone levels, this conclusion remains speculative.

2.2 Verbal & Visuospatial Thinking

The verbal and visuospatial cognitive domains discussed here are well known to use specific lateralized brain areas in the left (LH) and right (RH) hemispheres respectively (Andreano & Cahill, 2009). This is known as hemispheric specialization, and gives rise to so-called functional cerebral asymmetries (FCA). Women overall show a more dominant LH, which is thought to cause

their superior performance on verbal tasks. In men a more dominant RH has traditionally been linked to superior performance on visuospatial tasks, although this dominance and the exact nature of this advantage recently became, and continues to be a topic of discussion (Wallentin, 2009). Andreano and Cahill (2009) conclude that women show better cognitive skills overall, and argue that most of their advantages can ultimately be explained by whether women are able to use a cognitive strategy that incorporates their superior (LH) verbal processing. Their claim that men and women can have very different cognitive strategies in similar tasks is well supported by functional neuroimaging studies, that show distinct sex-related brain activation patterns (Hughdahl, Thomsen & Erslund, 2006; Weis et al., 2008; 2010; Pletzer et al., 2014).

2.2.1 Verbal

In studies on the COC, performance on LH lateralized verbal processing has often been assessed using a verbal fluency task that requires a participant to name as many words as they can in a short period of time (i.e. words from a certain semantic category, or starting with a given letter). Griksiene and Ruksensas (2011), in one of the few studies that actively accounted for the different progestins in the COC, indicated that pill users in general performed worse on letter verbal fluency. Pills containing *anti-*

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androgenic progestins impacted performance less severely than those containing an androgenic variety. An earlier study by Mordecai, Rubin and Maki (2008) had reported no influence of either COC use or MC phase, but their study did not account for the androgenicity of the progestagens. In light of Griksiene and Ruksensas (2011), this could explain the lack of results, as the grouping of androgenic and anti-androgenic COC users' scores might have leveled each other out. Gogos (2013) also did not discriminate between androgenicity of the progestins, and reported no significant differences on a picture naming and semantic verbal fluency task. Although insignificant, scoring patterns were congruent with their previously reported findings on memory performance (COC-users and high E2/P4 women outperforming low E2/P4 women and men). The findings of Griksiene and Ruksensas (2011) complicate previous findings on these measures, as any test not differentiating between pill users on androgenicity of the progestogenic components is then theoretically in danger of its results having been counterbalanced within the experimental group.

A neuroimaging study by Rumberg and colleagues (2010) required participants to

imagine speaking out freely associated verbs after seeing a noun. A test prior to the fMRI scanning session had shown no significant performance differences between COC users and NC women. During this task, scans revealed that COC users had relatively stronger activation of the right inferior frontal cortex (IFC) than non-users, which is more typical of male brain activity (Gauthier, Duyme, Zanca & Capron, 2009). The left IFC was more active in both COC users and NC mid-luteal high E2/P4 women compared to early-follicular low E2/P4 women and men. The left IFC is the site of Broca's area, which is a majorly important area for speech production.¹² More activation in any brain area is generally considered a sign of increased allocation of cognitive resources to a task, in this case language processing. This different activation pattern might be explained by an effect of the COC on interhemispheric communication; a topic we return to after we discuss the visuospatial domain. For now, it is clear that despite clear differences brain activity, behavioral effects of the COC in the verbal domain are less so, but variation in androgenicity of progestins warrants a critical look at past studies and for future research.

¹² This is one of the best known areas implicated in certain higher-order cognitive processes. Patients with lesions in these areas lose the ability to speak and have difficulty understanding

complex syntactic constructions. Temporary impairment of its functioning in healthy persons, by targeting the area with strong electromagnetic pulses through the skull (transcranial magnetic stimulation; TMS) elicits similar effects.

2.2.2 Visuospatial

In RH lateralized visuospatial processing, COC users have been mostly tested using a *mental rotation task* (MRT). The MRT requires participants to judge whether two similar or identical, but differently presented images are identical. It is assumed that before comparison is possible, some form of imagined rotation of one of the pictures is required to align them before the mind's eye. Performance on this task shows very clear sex-related differences, consistently favoring men over women (Andreano & Cahill, 2009). In NC women, visuospatial abilities correlates negatively with concentrations of E2 and P4. Performance on the MRT is best during menstruation, when natural E2/P4 levels are at their absolute lowest, and is worse during both follicular and luteal phases (Little, 2013).

Research in COC users by Wharton and colleagues (2008) showed that performance on the MRT was significantly impaired by an anti-androgenic progestin component, whereas it improved in androgenic pill users. Contrastingly, Griksiene and Ruksensas (2011) reported that androgenic COC users showed significantly worse performance on the MRT in comparison with anti-androgenic COC and non-users. Pletzer, Kronbichler, Nuerk and Kerschbaum (2014) performed a functional neuroimaging study on COC users using two *numerical* tasks. Numerical tasks and visuospatial tasks are thought to

primarily activate similar brain areas in the parietal lobes (Hubbard, Piazza, Pinel & Dehaene, 2005). Here, women using COC performed similarly to NC women in the low E2/P4 phase, and were outperformed by men, and women in high E2/P4 phases of the MC. Interestingly, pill users again showed brain activation patterns similar to men, with more activity in RH frontal areas (similar to Rumberg et al., 2010). Pletzer and colleagues (2014) conclude that androgenic effects of the pill should be considered the cause of the masculinized brain activity, but that lowered E2/P4 levels are more likely the cause of the behavioral effects.

It is worth investigating further whether differences in performance arise between active and inactive pill days to see whether pill androgenicity determines effects on the short term. Support for such a hypothesis is provided by Aleman and colleagues (2004), in a study where a single oral administration of the most androgenically active steroid testosterone (T) in females was found to improve performance on the MRT (Aleman, Bronk, Kessels, Koppeschaar & Van Honk, 2004). The consistently suppressed T levels in COC users (Zimmerman et al., 2014) might then also explain some of the reported negative effects on MRT performance observed in Wharton (2008), but still does not account for the inverted outcomes reported by Griksiene and Ruksensas (2011). Additionally, endogenous T levels in saliva

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samples of NC females or males previously predicted no performance differences (Puts et al., 2010), emphasizing that effects of long-term suppression of T cannot be readily inferred from the short-term effects of a single administration.

Findings on the effects of COC on visuospatial performance thus far appear highly inconsistent. While neuroimaging in pill users as well as in NC women during different phases of the MC consistently uncover changes in brain activation (Toffoletto et al., 2014), many behavioral studies have failed to find any significant behavioral differences on visuospatial tasks (Warren et al., 2014). This suggests current behavioral experiments are insufficiently able to target and elucidate the cognitive processes that are affected, or that differences on this cognitive domain are just small or non-existent.

2.3 Summary

It is generally accepted that sex-

hormones in women can affect cognitive performance. It is currently far from evident what direct psychoactive effects synthetic hormones have, or whether they only affect cognitive performance through the suppression of natural hormone levels. Effects of the latter are well established in naturally cycling women, and both have been found to affect brain activity as well as brain structures on the long term. Interestingly, some effects vary with type of progestin used in the pill, but studies on this are few and produce mixed results. This is also the case in general for the pill, with some of the most visible differences in the domains of memory, verbal and visuospatial cognition. Successful outcomes are however still far and few between, with some major studies having even reported no cognitive effects whatsoever (Islam, Sparkes, Roodenrys & Astheimer, 2008), so more original research and replication studies are highly necessary.

3. Effects of the COC on Social and Emotional Functioning

3.1 Negative Mood and Stress

Although population studies into the mental health effects of the COC have not confirmed major negative side effects (i.e.

Duke, Sibbritt & Young, 2007; Skouby, 2010), negative mood effects and even depressive

symptoms are reported in some users. In a double-blind study by Gingnell and colleagues (2013) it was found that in women who had previously experienced such negative effects, depressive symptoms increased when these women were given the pill. Much remains unclear as to which component of the synthetic steroids in the

COC might cause such symptoms. It is well documented that lowered levels of natural estradiol (E2) - such as in COC users - could lead to depression, as is seen in some women after pregnancy or when approaching menopause (Brummelte & Galea, 2010; Schmidt et al., 2000).

The link between negative symptoms, depression and lowered levels of endogenous E2/P4 may in part be explained by the role of estradiol in a psychological process called *fear extinction*. This is the natural process of 'unlearning' an association between a neutral event and a negative experience that instilled a fearful associated memory of the neutral event.¹³

Two brain areas that are highly involved in the formation and activation of fear extinction memories are the amygdala and the hippocampus. The amygdala has been found to play an immensely diverse role in the experience of emotion, as well as forming and 'reliving' emotional memories (Phelps & LeDoux, 2005). The hippocampus as a whole has long been considered the place where non-emotional memory information is stored (Yonelinas, 2002), but more recent research has unveiled a distinct role for the anterior hippocampus in certain

negative emotional behaviors (Fanselow & Dong, 2010). Healthy functioning of this network appears dependent on estrogen levels. Walf and Frye (2006) for example reported that blocking estrogen receptors in the hippocampus (but not amygdala) increased fearful behaviors in rats. Consistently, a study by Zeidan (2011) found rats that were given (natural) E2 during or quickly after the 'unlearning' of a negative associated memory exhibited better fear extinction a day after the process.¹⁴

Zeidan (2011) and Graham (2013) also tested naturally cycling women, and both found that women in their high-E2/P4 phases in the menstrual cycle showed improved 'unlearning' (*fear extinction recall*) compared to those low in E2/P4. Graham (2013) conducted similar experiments on pill users, as well as on rats who were given the COC, and found that these groups also displayed impaired fear extinction recall. In rats, a subsequently administered dose of E2 alleviated this impairment. This is one of very few studies that provides direct support for differential behavioral effects of natural estradiol (E2) and synthetic ethinyl estradiol (EE) contained in the COC. Furthermore, in line with all the aforementioned studies it

¹³ In many studies, such as Zeidan (2011) and Graham & Milad (2013), this is done by training animal or human subjects that observing a light switching on means that an electric shock will follow. 'Unlearning' is then achieved through presenting the light (CS) without giving the

associated shock. Sufficient training in healthy test-subjects then leads to the old association diminishing in strength, as the new, unfeared association gains in strength.

¹⁴ Results on a longer time scale were inconclusive.

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supports the idea that diminishing of E2's effects by overall suppressed endogenous levels can increase negative emotions in pill users.

In a DTI¹⁵ neuroimaging study, De Bondt and colleagues (2013) reported higher densities of the fornix in COC users. The fornix is a bundle of nerve-fibers that connects the hippocampus and the hypothalamus, and its thickening is thought to reflect increased capacity for neural communications. Among other things, the fornix is involved in episodic LTM¹⁶ (De Bondt et al., 2013), which - from a cognitive perspective - can easily be argued to be involved with many aspects of emotional functioning. The hypothalamus is an area that is highly involved in maintaining homeostasis. It regulates bodily responses to emotive stimuli, and influences the formation (as well as retrieval) of memories in the hippocampus (LaBar & Cabeza, 2006). Nielsen and colleagues reported COC users' memory for emotionally laden pictures (2011) and stories (2012) was better than in non-users. It is unclear whether the materials

that were used in the experiments were negatively valenced. If that is the case - which is well possible¹⁷ - this is consistent with the impaired fear extinction effect reported by Zeidan (2011) and Graham (2013) (-worse 'unlearning' or 'better' memory?). However, their finding that emotional responses in pill users are blunted - suggestive of suppressed emotional processing - does not clarify matters.

A possibly related explanation for negative effects associated with COC use may be sought in its influence on cortisol. Cortisol is also known as the stress-hormone, and it activates many systems involved in fight-or-flight responses¹⁸, including in the brain (i.e. increasing attention, heightening the senses). Nielsen and colleagues (2011; 2012) observed higher endogenous cortisol levels in COC users than in non-users. Their studies reported that saliva samples of women using COC's showed significantly less increases of cortisol after exposure to emotionally arousing pictures and a physical stressor¹⁹. In one experimental study, COC users who were given a dose of cortisol

¹⁵ Diffusion tensor imaging; a technique that allows for rough tracking of neural tracts from MRI data.

¹⁶ Episodic memory is about recalling experiences from past life-events, as opposed to for example factual or procedural knowledge unrelated to personal experience.

¹⁷ It is generally thought negative emotions elicit the strongest, as well as most predictable and well-known brain and behavioral responses. Therefore, these emotions have received by far the most attention in contemporary studies

(Lindquist, Wager, Kober, Bliss-Moreau & Barrett, 2012).

¹⁸ In biological terms: It activates the central nervous system's sympathetic systems, which reroutes energy to processes in preparation of fight or flight. In doing so, it downregulates other bodily processes, such as the digestive system, making continuous stress unhealthy for normal functioning.

¹⁹ In this experiment, this consisted prolonged exposure of the right hand to ice cold water.

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showed greater increases in blood plasma levels than NC women, with higher levels remaining active in the body for a longer period of time (Gaffey, Wirth, Hoks, Jahn & Abercrombie, 2014). This suggests pill users are affected stronger and longer by stress. It is widely accepted that cognitive performance can suffer from high sensitivity to stress hormones. These findings are corroborated by studies on the stress-protective effects of E2 (Ter Horst, Wichmann, Gerrits, Westenbroek & Lin, 2009), which is suppressed by the COC. The blunted stress responses reported in Nielsen (2011; 2012) might then be explained by the heightened 'normal' cortisol levels in these women, having brought the stress-response systems already closer to functional saturation. Exposure to external stressors - even if that further increased cortisol - would then no longer cause the emotional response as it would in women with lower baseline levels.

3.2 Mating and Relationships

If there is one aspect of human behavior where one's sex-hormones are rightfully often said to be 'playing up', it is in sexuality and mating behaviors.²⁰ Such effects are clearly observed when investigating brains

and behaviors in women around ovulation, or during other, non-fertile stages of the MC (review: Alvergne & Lummaa, 2010). In their most fertile periods (high E2), women show increased preference for male faces that display signs of high testosterone levels. Especially estradiol appears to modulate this behavior, with the low E2 levels in COC users accompanying similar behavior as in low E2 NC women; a preference for more feminine faces (Roney & Simmons, 2007). It is unknown whether EE levels influence this behavior, yet again it seems no functional substitution takes place.

Another difference is found in women's preferences for male body odors. Ovulating women prefer smells of males who are physically 'symmetrical' (which biologists consider a marker for fitness) and who genetically differ strongest from their own constitution (Thornhill et al., 2003). Women using COC show the opposite behavior, preferring smells of more genetically similar men (Wedekind, Seebeck, Bettens & Paepke, 1995). Pill use additionally affects women's attractiveness to men, as women's body odors are rated more attractive during ovulation, which is never the case in COC users (Kuukasjärvi et al., 2004).

In light of these findings, Roberts and colleagues (2012; 2014) investigated how

²⁰ This was cunningly illustrated by Ronay and von Hippel (2010), who found that in male skateboarders performing tricks, the presence of

an attractive female experimenter resulted in increased testosterone levels that correlated with higher risk taking.

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COC use affected women's relationships. In support of their 'congruency hypothesis', they found women who had been on the pill at the beginning of a relationship and ended using it somewhere along the way, rated their partners lower on attractiveness and sexual satisfaction. Inversely, partners were rated higher on their parenting skills. The latter is perhaps explained by COC-users' preferring more feminine males (Roney & Simmons, 2007), who, because of their lower testosterone levels, might have a stronger disposition to invest time in their offspring (Fleming, Corter, Stallings & Steiner, 2002; Gray, Kahlenberg, Barrett, Lipson & Ellison, 2002). On average, relationships of ex-COC users lasted longer than of never-users, and with lower chance of women ending them (Roberts, 2012).

Cobey, Roberts and Buunk (2013) found that women who switched between pill usage and non-usage during a relationship reported increased feelings of jealousy toward sexual rivals, regardless of the direction of change. COC users also had higher baseline levels of jealousy, but this finding is somewhat limited by the fact that MC phase in NC women was not accounted for (as high fertility phases also increase jealousy). Welling and colleagues (2012) had previously reported that EE (but not progestatin) levels positively correlate with frequency of mate retention tactics in women using COC; specifically in behaviors aimed at

their partners, instead of at female (sexual) rivals. Piccoli, Foroni and Carnaghi's (2013) research suggests the latter behavior may be stronger in (high E2) fertile NC women, who in their experiment displayed stronger dehumanizing attitudes toward other women than (low E2) non-fertile women and COC users.

3.3 Summary

Although overall risk of negative consequences is small, in some users the COC does have profound effects on mental health. A reasonable explanation for this may be the lowered E2 levels in users, which in normal people is thought to have stress-protective effects. Furthermore, pill use deteriorates users' ability to forget a previously negatively associated memory with a random neutral event, but also lowers subjects' sensitivity to (physical) stress inducers. On another note, the pill has been found to have a large influence on females' mating and relationship behaviors, with notable effects in mate preferences. Interestingly, the pill has been found to cause changes in certain romantic partnership dynamics, but these occur primarily after switching (taking up or ceasing) use during the course of a relationship. Effects of the COC on social behavior appear to extend to other (non-romantic) relations as well, but research on that topic is scarce and not further dealt with here.

4. Effects of the COC on Interhemispheric Dynamics

Studies have often reported significant differences in neuro-morphological (Pletzer et al., 2010) as well as psycho-physiological²¹ (Weis et al., 2008; 2010) asymmetries over the course of the menstrual cycle. It is thought the sex hormones play an important part in these phenomena. Performance differences in COC users on the verbal and visuospatial domains discussed previously may well be caused by changes in neural signalling between the cerebral hemispheres (as do some effects on emotional processing). Such signaling is considered to be at the root of functional cerebral asymmetries (FCA)²², but there are different views on what type of interhemispheric communications cause these (see: Bloom & Hynd, 2005).

Some argue that cognitive FCA's are caused by certain dominant brain areas (that are best equipped for a task) suppressing interfering neural activity in the lesser-equipped hemisphere through inhibitory

signaling, which results in more lateralized but optimal performance (Chiarello & Maxfield, 1996). This is called interhemispheric or transcallosal inhibition (TCI), after the inhibitory neural signals that traverse the corpus callosum (a body of neural tracts connecting the two hemispheres). It is very clearly observed in the motor cortex, where both behavioral as well as well as psycho-physiological experimental measures (fMRI, TMS) have revealed such a mechanism (i.e. Schutter, 2009, p. 249).²³

One study that tested specifically for alterations in cognitive FCA's in COC users was conducted by Cicinelli and colleagues (2011) with a visuospatial line bisection task. In the task, subjects are asked to split three horizontal lines in half using their preferred hand, and it is measured whether deviations from the absolute middle occur. Healthy right-handed people are generally found to deviate slightly to the left of the middle,

²¹ Bridging these modalities is often conducted in experiments where certain mental processes are elicited ('thinking about X') while monitoring changes in physiological processes in the brain. After sufficient repetition, researchers carefully attempt to establish a link between the two, about what cognitive processes are reflected in certain neural activation patterns.

²² This term is used for task specific hemispheric asymmetries that are observed in cognitive performance, but also in neuroactivational

measures.

²³ From a behavioral perspective, such a mechanism is intuitively clear when performing the following task: rubbing your right hand in a circular motion across your belly, while your left hand is patting your head. These different motions appear to interfere strongly with each other, while bottom-line each motion originates from neural activity in motor areas in separate hemispheres.

whereas left-handed people deviate slightly to the right. Right handed COC users were found to display a small but significant increase in leftward bias, which the authors argued is the result of improved interhemispheric communication. This conclusion is inconsistent with theorizing by Hausmann, Weis and others, who maintain that greater FCA's reflect more optimal processing, yet others take it to reflect an improvement in interhemispheric interaction (Little, 2013; Gogos et al., 2014; Warren et al., 2014).

Hausmann and Güntürkün (2000) posed the theory that P4 levels modulate inhibitory signaling between the hemispheres. This means that less dominant hemispheres become more active when P4 is higher. Such was indicated by lateralized cognitive performances (i.e. faster recognition of words in the right vs left visual field) and later compounded by neuroimaging results, with similar but weaker

5. Final remarks

Research on the effects of the pill has revealed a number of effects on the brain, cognitive and social-emotional behaviors. Studies have uncovered some elements of semantic and emotional memory to improve, but also a deterioration in the unlearning of negative emotional associations. Altered brain activity occurs in verbal and visuospatial tasks, as well as in general

effects found for E2 (Weis, Hausmann, Stoffers & Sturm, 2010). Neuroimaging studies that tested specifically for verbal as well as visuospatial processing in NC women also reported that interhemispheric inhibition and FCA's are modulated by E2 and P4 levels (Weis et al., 2008; 2010). Two previously mentioned functional neuroimaging studies on verbal and visuospatial performance indicated that COC users had relatively stronger brain activity in the RH frontal regions, opposite from the (female dominant) LH language centers of the brain. In Rumberg et al. (2011) the simple pretest had shown no differences in any group on verbal performance, but in Pletzer et al. (2014) performance by COC users on the visuospatial task was on par with low E2/P4 women. (These results are again suggestive of no functional substitution of E2/P4 taking place in COC users, instead showing effects reminiscent of those naturally low in endogenous levels.)

changes in cross hemispheric communication, with users showing more male-like brain activation. This is accompanied by behavioral changes, but these are small, sometimes inconsistent and little tested. During pill use women's mate preferences change, affecting interrelationship dynamics strongest when switching regime over the course of a

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relationship. Most research on the cognitive and social-emotional effects of the pill suggests the main effects are caused by lowered levels of endogenous sex-steroids. Subtle direct effects of the synthetic hormones are found in some cases, some of which relate to progestin androgenicity. Cognitive and emotional effects overall are small, and results mixed between studies.

Many researchers have remarked on the lack of standardized testing, but also the small variety of tested cognitive, social and emotional functions, making drawing strong conclusions on the current literature undesirable. Nevertheless, the large differences caused by the pill on the physiological level warrants much more research.

Chapter 4

Population studies approach

Interdisciplinary remarks

Population studies in the context of this thesis on the use of contraceptives, is not a set discipline, but more of a category to refer to concerning research into the broad workings of society. This category will include research from authors from multiple areas including population geography, demography, population sociology, economy and medical sciences. Since these domains generally use relatively similar methods, especially in the context of biomedical research and behavioral neuroscience, we will view, mainly for pragmatic reasons, population studies as a single discipline. We are aware of the fact that in reality it may not be perceived as a single discipline, however, as we are comparing population studies with the other disciplines solely on the basis of their research methods, which in the case of research used from population studies is rather similar, we believe it is justified to view it as one discipline.

In population studies a variety of methods is used for research depending on the subject. The biggest difference between different forms of research is whether it is correlational or causal, of which the former is

most used. This is due to the fact that a lot of societal research is based on data that might not have been gathered for that specific research. For instance, databases of general information are often used and then examined to find correlations between different factors. Depending on the subject, surveys can also be used to gather data leading to a better possibility to make statements about causality. Since societal research rarely takes place in a controlled laboratory environment, causal relations are rarely established and some form of inferring is used most of the time to develop theories on the basis of correlational evidence. In some cases, models are developed and compared to reality in the search for causality.

The importance of the aforementioned for this thesis is that the bulk of the research papers used are either based on theories based on correlational evidence, leaving a lot of room for the interpretations of the author(s), or are merely examining statistical data from different countries/regions while only being able to provide suggestions of what the reasons for differences in data may be. Although statistical analyses is often used, please be aware that, in most cases, this does not say

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anything about causality, but merely confirms a correlation between two factors. Since the experiments have not been carried out in an controlled environment, causality can often not be proven although it might be perceived as such by the reader. Another consequence

of the fact that there is room for inference is that different authors come to different conclusions on the basis of the same evidence. This makes it especially hard to come to 'hard' facts making suggestions more common.

Effects of the hormonal birth control pill on female life choices and society

Pim van den Brink - Population studies

Key points

- The pill put the fertility decision of its users solely into the hands of women.
- The pill did not directly cause a decline in fertility, but by being far more reliable than its predecessors, the pill gave women more power to control their fertility.
- The reduction of the risk of undesired pregnancy caused by the pill led to its users investing more in their education and career.
- Pill use is partly determined by social norms and attitudes, but at the same time influences these norms, contributing to the changing of women's roles in society and societal attitudes towards sexuality and fertility.
- Pill usage varies greatly between and within countries, depending on religious, social and cultural attitudes towards fertility and fertility control, sexuality, gender roles, socio-historical developments, and access to contraception. However in general:
 - Higher educated women tend to use the pill more
 - Younger women tend to use the pill more
 - Women from less deprived areas and a higher socioeconomic status tend to use the pill more

In this section, we consider the effects of the hormonal birth control pill on the life choices of individual women and the aggregated effects of these choices on society. We will start by describing the historical introduction of the pill and its corresponding societal context. Thereafter we examine the effect of the pill on fertility and individual female life choices and the implications of these choices. We then analyze the factors determining pill use and use a case example of pill use in Europe to examine the differences between countries. We end this section by looking ahead at how these insights relate to the final answer to our main interdisciplinary research question: To what extent has the birth control pill had a positive influence on women in western societies. Although some effects of the pill seem to apply for most countries, please be aware of the fact that most data are based on the results of country specific research, which might limit its applicability to other countries, making it harder to make statements about 'society' in general.

Methods

In order to find secondary data regarding the effects of the pill on society first a preliminary literature search was conducted using publications found through the Google Scholar and Web Of Science online search engines. Key search terms included: combined oral contraceptive, birth control pill, family planning, health, demography, geography, fertility, society [...], or any combination/derivative of the aforementioned. This generated a limited number of applicable research articles from a number of different research fields including: geography, demography, sociology, economy and gynecology. When starting this study, we aimed at using disciplinary insights from human geography to describe the effects on society. However, since the publications found in the preliminary literature search ranged from such a large number of fields, we felt we could not justify still calling these insights coming from human geography. As explained in the preliminary remarks, we use the term population studies to describe the overarching field of which the used publications originate from.

1. Historical background

The origins of combined oral contraceptives lie in the late fifties and early sixties. At the end of the fifties the first generation of oral contraceptives had already been developed, but it took until 1960 for the first birth control pill, called 'Envoid', to be approved by the Food and Drug Administration in the USA (Bailey, 2006). Since then, the birth control pill quickly spread across the (particularly developed) World and is currently being used by more than 100 million women worldwide (Mosher & Jones, 2010). Usage of the pill has been relatively stable in the past decades for most developed countries, although there have been some short periods of decline of pill usage after negative publicity about possible health effects (Leridon, 2006., Ketting & Visser, 1994). Despite its widespread use, the pill has certainly not spread equally across different countries. Even between developed countries there is a large difference in the preferred contraceptive, where in some countries pill usage is almost as high as 50 percent while in others it does not even reach 15 percent (Leridon, 2006., Skouby, 2004., Spinelli, 2000).

Although the pill entered the contraceptive market in the USA in the early sixties, it was initially not available for all women. In the beginning only married women had access to the pill who needed to visit a doctor in order to get a prescription,

which reflected the societal attitude towards sexuality and fertility at the time, and there was, at least in the USA, a strong catholic lobby against the liberalization of access to the pill and contraception in general (Bailey, 2006., Goldin & Katz, 2002). Goldin and Katz explain that the restricted access to the pill for unmarried women was caused by a combination of both legal and social factors. However, this limited access was all about to change as the introduction of the pill coincided with (and influenced) other social changes which radically altered the position of women and the attitude regarding sexuality and fertility. As Bailey writes: "The introduction of the pill corresponded with the resurgence of the women's movement, the spread of labor-saving household technologies, the enactment and enforcement of antidiscrimination laws". All these factors combined led to a slowly increasing acceptance of family planning and pill use. The increased acceptance of family planning services and provision to minors, in its turn also reinforced the changes in community norms (Goldin & Katz, 2002). In the USA, the changes in the social norms were reflected in changing laws regarding contraception and pill use. Eventually the age of majority was lowered (this was actually the result of societal disagreement over the fact that minors could fight in the war in Vietnam, but it lies outside the scope of

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this thesis to elaborate further on this matter) and women were able to access the pill without needing parental consent which resulted in, according to Bailey, an empowerment of young women under 21. Although the circumstances differ from country to country the example of the USA can give some insight into how the introduction of the pill broadly went in countries where pill use is now relatively high.

To indicate these similarities in the western world, Ketting and Visser (1994), who researched the contraception use in the Netherlands, seem to show that there was a similar situation in the Netherlands where they distinguish a number of interacting factors which stimulated the acceptance of family planning as they write:

“Strong acceptance in family planning was influenced by changing values regarding sexuality and the family, the transition from agricultural to industrial society, rapid economic growth, declining influence of the churches on daily life, introduction of mass media and increased educational level.” (Ketting and Visser, 1994)

Here has to be noted that there were special circumstances in the Netherlands which together accelerated the acceptance of family planning. These factors were a combination of a relatively strong family planning movement, fear in the general public of excessive population pressure on available space and a positive influence of

health care services as general practitioners felt highly responsible for the fertility wishes of their clients and there was a very strong support from the public health care insurance system (Ketting & Visser, 1994).

Visser and van Bilsen (1994), also highlight the importance of sex education and family planning services in the increasing use of contraception and changing social norms. According to them, sex education and family planning services are important whilst they increase the amount of knowledge about sexuality and birth control. Knowledge in its turn has a positive effect on the effective use of contraception by women. Although, knowledge is increased by sex education, it is in itself not sufficient to change the behaviour of young men and women (Visser & van Bilsen, 1994). Social norms themselves also play a crucial role in contraceptive behavior where a social norm is defined by Visser and van Bilsen as a: “perceived influence of people or authorities important to the individual and whose opinion tends to matter to him or her”. For instance, sex education won’t serve its intended purpose if sexuality cannot be discussed outside school indicating the important role (and responsibility) that parents have. Sex education also influences social norms as it makes the attitude of adolescents more liberal and tolerant regarding sexuality (Visser & van Bilsen, 1994).

In general one might say that the introduction of the pill and pill use was, and maybe still is, determined by social norms

and attitudes, but at the same time also influences them. But what was the exact effect of this introduction of the pill?

2. The pill and fertility

Since the pill has been introduced there has been a remarkable decline in the number of children born per women worldwide (Leridon, 2006., Ananat & Hungerman, 2012., European Society of Human Reproduction and Embryology [ESHRE], 2001). Most sources on this issues give slightly different explanations for this phenomenon, although most authors claim that there is no direct link between fertility and pill use. For instance Leridon claims that: "At the country level, the conclusion is unambiguous: within individual countries, there is no systematic negative correlation between fertility and contraceptive pill use." and Ananat and Hungerman state: "Over time, the pill had no effect on total childbearing". According to Leridon, the pill has certainly played its part in the reduction of fertility, but it was never a reason for the decline in fertility. He gives multiple arguments supporting this statement. First of all, the decline of fertility in developed countries has started way before the pill was even invented in the late fifties (Leridon, 2006). Therefore the pill can never have caused this decline. Furthermore, if you look at Europe for instance, there are multiple countries where pill usage is low, but fertility

is equal to, or even lower to that of other European countries (Leridon, 2006). This is not to say that in individual countries the pill did not influence, and maybe accelerated the fertility decline, however when looking at western societies as a whole the pill cannot have been the sole cause of declining fertility. But if the pill did not cause fertility to drop, what did?

In general three categories of factors can be distinguished playing a role in the declining fertility. The first are economic factors such as a rise in general welfare and the emerging labor opportunities resulting in the rise in demand for labor in, especially the service sector, in which a lot of women are nowadays employed (Bailey, 2006., Leridon, 2006). In the view of the ESHRE (2001) the decline of fertility has everything to do with the fact that most couples want less children and according to the ESHRE the amount of children that a couple wants is not set by psychological factors, but is strongly related to the ability to raise your children at the same standard as you were raised yourself. They write: "the income of prime aged adults sets the desired standard of living, against which they evaluate the ability of their own

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earnings to support a family” (ESHRE, 2001). So, seen from a purely economic perspective, an important economic factor is not the actual income, but the income relative to that of a couple's parents. The second category includes social factors such as cultural change leading to more individualism and secularization (which reduced the impact of religious pro-natalistic norms) and in a lesser degree, the rise of feminism (Goldin & Katz, 2002). Feminism made women view themselves as equal to their male counterparts and this in turn increased the likelihood of young women believing they could aim for the top. The ESHRE indicates the importance of social and economic factors stating: “The most likely reasons for declining birth rates are clearly social and economic rather than medical” and any social trends in the amount of wanted children per couple have taken place entirely independent of any health care factors. The final category are technological factors leading to new or improved, more reliable, contraceptive technologies and better access to those technologies (Leridon, 2006., ESHRE, 2001). To indicate the improvement in reliability, the pill decreased the likelihood of becoming pregnant fivefold compared to the male condom and the annual contraceptive failure for birth control pill users is between one and two percent (Hock, 2007). So despite not being directly responsible for the start of the decline in

fertility, the pill did contribute to the fertility reduction by making it easier to control fertility reliably, preventing unwanted pregnancies and, as a side effect, thereby lowering for instance the abortion rates (Ananat & Hungerman, 2012). In short, most arguments given for the decline in fertility belong to either economic, social, or technological factors, and as Leridon states: “ideally, a full analytical model should include all these factors”.

Although, the pill might not have been the cause of the reduction in overall fertility, initially it did change the average characteristics of the children born. Ananat and Hungerman (2012) explain that in the USA, the introduction of the pill resulted in an increase of the relative amount of children born with low birth weight and the relative amount born in poor households. This was due to the fact that more educated women tended to use the pill more and used it to postpone having children (ESHRE, 2001., Goldin & Katz, 2002). In the long term the effect of low birth weight and more children in poor households did not show, according to Ananat and Hungerman because: “Immediate fertility reduction reflects the postponement of above average-quality births” and they argue that the characteristics of the children which were eventually born to women who initially postponed pregnancy did not worsen. The relationship between the pill and overall fertility have now been

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discussed, but what are the consequences of the introduction of the pill on the level of

individual life decisions?

3. Effects on individual life choices

Women who were using the pill postponed their first child because they wanted to be able to increase their marital and educational investment (Ananat & Hungerman, 2012., Bailey, 2006). So women did not want less children because of the pill, but were able to time childbearing better enabling them to invest in their education and career. This delaying effect on pregnancies of the pill is shown, according to Bailey, by the fact that the pill reduced the likelihood that a woman would be a parent at age 22 by 14-18%. A consequence in the long run of the increase in marital and educational investment was that it led to an increase in the chance that a child had a married mother which had a college degree (Bailey, 2006).

By being very reliable the pill allowed women to start a professional education without either having to practice abstinence or deal with the uncertainty of a possible pregnancy (Goldin & Katz, 2002., Bailey, 2006). Goldin and Katz (2002) seem to agree by claiming that: "The pill directly lowered the costs of engaging in long-term career investments by giving women far greater certainty regarding the pregnancy consequences of sex". Hock (2007) adds that "the declining early fertility was the

proximate link between early contraceptive access and increases in educational attainment" and "greatly increased the likelihood of staying in college". Bailey even calls the fairly costless birth timing the pills most important contribution.

In addition, the pill allowed women to postpone becoming pregnant in a life phase which is crucial to their education decisions, since college is the time when career, marriage and family planning decisions are/were made (Hock, 2007, Bailey, 2006). As more women invested in education a larger share of women entered the labor market whilst at the same time there are more uncertainties in this market (ESHRE, 2001., Bailey, 2006). The result of this was that, for instance, the female labor participation for women between age 26-30 increased by 8% in the USA (Bailey, 2006) and pill usage also had a positive effect on the share of women who are employed in nontraditional professional occupations (Goldin & Katz, 2002). As an example, this can be seen in the larger number of women who practice law and medicine. There has to be noted however, that only the women who actually delayed childbearing, were working more in the labor market (Bailey, 2006).

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Taking care of your children means that you make less money by working, and the fact that the female labor participation rose meant that they were earning more (also relative to men) which made the amount of money 'lost' by getting children at a young age higher (ESHRE, 2001., Hock, 2007). In this sense, early fertility is of great influence on the (human) capital accumulation capabilities of women (Hock, 2007). As mentioned by Hock: "the pill acted as a catalyst in allowing women to implement a more optimal plan of fertility and human capital investment". The fact that women delayed childbearing did not only have an effect on the educational and career opportunities of women. College is very expensive and costs a lot of time. Thereby, the ability of men to invest in their education might also be reduced after they get a child. As their partners are able to postpone childbirth, the pill as a result may have also influenced the educational outcomes of men (Hock, 2007).

The fact that women invested more in their education and career also led to women starting to marry at a later age, and the amount of women who never married increased, in part due to the fact that they were studying longer and pursuing careers (Goldin & Katz, 2002). For instance, Goldin and Katz in their study mention that having

access to the pill at age 17 had a seriously decreased the chance that a woman was married at age 23. Since more women were pursuing a career, women investing in their education slowly became more wanted marriage partners and so the marriage market for career women "thickened" (Goldin & Katz, 2002). Goldin and Katz finally add that: "the pill could then produce a new equilibrium in which marriages are later, careers are more numerous, and matches are "better." When marriage is delayed, mismatch in the marriage market, a potential career cost, is reduced.

Apart from influencing marriage decisions the pill also affected the way people dealt with sex ²⁴, eventually contributing to more liberal attitudes towards sex, especially in countries where pill usage is high (Leridon, 2006., Visser & van Bilsen, 1994). Although there are numerous of other methods available for preventing women to become pregnant, the pill had some specific characteristics that those other methods did not have. First of all, it puts the fertility decision solely into the hands of women. Before the pill, women always needed to discuss any contraceptive choice with their male partners as with, for instance, the use of a condom. The pill gave women the power to control their fertility irrespective of their male counterparts (ESHRE, 2001, Skouby,

sexual interactions outside marriage.

²⁴ This entails sex within marriages as in

2004). Furthermore the pill decoupled the relation between fertility and sex (Goldin & Katz, 2002., Leridon, 2006). It allowed couples not having to marry why still being able to have sex (Goldin & Katz, 2002). As Goldin and Katz put it: “Sex no longer had to be packaged with commitment devices, many of which encouraged early marriage”. Whereas most other methods available before the rise of the pill needed some form of action directly before the moment of intercourse, putting a heavier strain on personal discipline greatly decreasing the reliability of these methods, the pill requires

4. Factors determining pill use

When discussing factors that determine pill use, you must always keep in mind that the situation differs from country to country. As will be discussed further on, there are a number of country specific factors, such as religious, social and cultural attitudes towards fertility and fertility control, sexuality, gender roles, socio-historical developments, and access to contraception which influence pill use. However, even in countries where pill use is relatively low we can see that certain characteristics seem to be somewhat universal in determining pill use. However, there must be noted that, although most factors are presented here separately, in reality these factors are highly intertwined and it is often the combination of factors

no action during intercourse (Leridon, 2006, Bailey, 2006). Combined with better sex education, the influence of the pill on sex has influenced societal attitude towards sexuality and the nature of marriage and other forms of union (Leridon, 2006., Visser & van Bilsen, 1994). Visser and Van Bilsen do add that the pill did not have any impact on sexual behavior itself, only on the consequences of having sex. We have now seen what the impact of the pill was on individual life choices, but what determined whether women would start using the pill?

which is determining pill use. These factors are relevant for answering our research question since they contribute to the distribution, and thereby the possible impact, the pill has on society.

Age

The first, somewhat obvious factor, related to pill use is age. The age of a woman is of significant where women who are older tend to make less use of the pill, and make more use of female sterilization (Bentley et al., 2009., Mosher & Jones, 2010., Ruiz-Muñoz et al., 2012). Furthermore, at least in Europe, there are relatively more women over 40 who do not use a reliable contraceptive method (Skouby, 2004). However, age is a

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correlational factor as for instance, Fiebig et al. (2011) put the influence of age in perspective by mentioning that: “life stage rather than age, drives contraceptive decisions” supported by the fact that life stage is related to parity. Somewhat obvious Ruiz-Muñoz et al. (2011) note that: “Women who already have the number of children they want may, therefore, use more contraception, whereas those who do not yet have children or do not have the number they want may be trying to get pregnant”. In addition, as women get older the chances of them becoming pregnant decrease significantly making the concerning pregnancy it is also important how a woman perceives the risk of becoming pregnant and her attitude towards motherhood in determining contraceptive use (Dixon, Herbert, Loxton & Lucke, 2014). Although also somewhat self-evident, whether you are living with a partner and the fact that you are currently or formerly married also influences pill use. Women who are or were married tend to make less use of the pill compared to women who are cohabiting or never married (Mosher & Jones, 2010). Ruiz-Muñoz et al. (2011) add that: “Living with a partner can affect women’s contraceptive use, not only by predicting sexual intercourse but also because these women can share

contraceptive decision making with their partners, which may not be the case for those who have sporadic relationships”.

Education

An additional factor which most available research points out as an influence is the educational level of women, where women with a higher education tend to use the pill more often than women who are less educated (Bentley, Kavanagh & Smith, 2009., Fiebig, Knox, Viney, Haas & Street, 2011., Mosher & Jones, 2010., Ruiz-Muñoz, Pérez, Garcia-Subirats & Díez, 2011., Ruiz-Muñoz, Pérez, Gotsens & Rodríguez-Sanz, 2012). Mosher & Jones also add that, at least in the USA, lower educated women tend to use female sterilization more frequent than higher education women who tend to rely more on oral contraceptives and Ruiz-Muñoz et al. (2011) also suggest a relationship between level of education and childbearing patterns.

Socioeconomic background

Apart from education a woman’s socioeconomic background also seems to play a role in determining pill use and there have been multiple studies into the relationship between social background and contraception/pill²⁵ use and sexual behavior

²⁵ Some studies only looked at general contraception use and some studies only looked

at pill use specifically. As the pill is of course a form of contraception, general contraception use is related to pill usage.

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in general. For instance, Bentley et al. (2009) investigated pill usage in the UK and came to the conclusion that a large part in the variation of pill usage stems from the differences in socioeconomic position that these women are in. According to Bentley et al. this personal socioeconomic characteristic interacts with the geographic area in which women live. Here it is notable that contraceptive use in general is not distributed equally geographically, where contraception use is lowest in more deprived areas. In addition, the pregnancy rate in these deprived areas is also higher. The pregnancy rate seems to be correlated to the contraceptive use as, for instance, teen pregnancy rates are reduced as the contraceptive use increases (Ketting & Visser, 1994). Furthermore, the sexual activity amongst teenagers differs when comparing teenagers from lesser deprived areas with those of more deprived areas. Women with a lower level of education who come from a lower socioeconomic class and came from more deprived areas tended to have sex at a younger age and used less contraception during first intercourse, which is strongly correlated with pill use later in life (Ruiz-Muñoz et al., 2011., Ruiz-Muñoz et al., 2012., Mosher & Jones, 2010). The influence of social background is also confirmed by Mosher & Jones, who saw that in the USA pill usage was more frequent under white women than under black and Hispanic

women, and by Ruiz-Muñoz et al. (2012) as, in Spain, individual socioeconomic characteristics are strongly associated with contraceptive use where women from the lowest socioeconomic position use the least effective methods. Furthermore Ruiz-Muñoz et al. also distinguish political factors of being of influence on contraceptive use as they determine sexual and reproductive health policies and showed that your cultural background, according to them mainly constituting your country of origin and your religion, influence your contraceptive behavior, especially during first intercourse (2011). This influence of cultural background is confirmed by Bentley et al. (2009) who agree with the fact that religion seems to be of influence on your contraceptive behavior and Fiebig et al. (2011) who mention that language spoken at home also correlates with contraceptive use. To summarize what has been said so far, it seems that not only the personal socioeconomic characteristics are important, but also the socioeconomic characteristics of the places women live in play an important role in determining contraception use.

In contrast with the aforementioned, Du, Melchert and Schäfer-Korting (2007) who studied the contraception use in Germany, show that the relationship between socioeconomic factors and contraception does not seem to be strong in Germany as they state: "OC users did not

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differ from nonusers in most selected personal and socioeconomic factors”, although they did find that: “Residence in middle city and higher household income was found to be significant for OC use”. Interestingly, they also found that OC users tended to have a better health profile (Du, Melchert & Schäfer-Korting, 2007), which is interesting to combine with the conclusions of the biomedical sciences part. As Du et al. also realize themselves, since it is a correlational relationship between these two factors it is likely that there is a different underlying connection between health and pill usage such as general welfare. This is an example which shows the value of this interdisciplinary study as we, by integrating insights from biomedical sciences and population studies are able to make a causal connection²⁶ between pill use and health, but this will be discussed more elaborate in the integration section.

Barriers to access

A final factor determining pill use is the presence of potential barriers (Dixon et al., 2014., Fiebig et al., 2011). Dixon et al. looked

at barriers for contraceptive use in Australia and found five major barriers: side effects, lack of information, negative experiences with health services, contraceptive failure and difficulty with accessing contraception. All these factors negatively influenced the chance that a woman was using the pill. Furthermore, once using the pill, women were more reluctant to switch to other newer contraceptive methods which might explain the relative small proportion of women using these methods. Entwisle et al. (1997) confirm this as they note that there is a “preference for the known, familiar methods and sources over the unknown”. To sum up, education, social background, age and potential barriers all seem to play a role in determining pill use. However, as said before, these factors do not stand alone but are interacting. For instance, your socioeconomic background influence your chances of receiving proper education and the possibilities of experiencing barriers to access. Further, there is a large disparity in pill use between different countries even in the western world. In the next paragraph these disparities will be discussed.

5. What are differences between countries?

Since the possible amount of countries that can be compared is almost limitless, we have chosen in this paragraph to examine Europe

as an example, for practical reasons and because we believe Europe captures the difference that exist between the western

²⁶ There has to be noted that this is a

hypothetical conclusion which must be confirmed by further research.

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societies. In general contraception use in Europe is relatively high where oral contraceptives are currently the most widespread method, although there are large differences within Europe (Skouby, 2004). In a study done by Cibula (2008), which compared pill usage between fourteen European countries, it appeared that oral contraceptives are more frequently used in northern and western Europe compared to eastern and southern Europe (with the exception of the Czech Republic) (2008). Cibula mentions that: "Difference in OC use likely reflects religious, social and cultural attitudes towards fertility and fertility control, sexuality, gender roles and, to some extent, male attitudes towards contraception" adding that socio-historical developments, and whether women have access to contraception, may reflect some of the differences in pill usage. For instance, Kovacs (1997) found that, at least in the past, pill usage was relatively low in eastern Europe partly because the supply was insufficient and the pill had to be paid for whilst abortion was free (Kovacs, 1997., Cibula, 2008). Skouby, who examined pill usage in France, Germany, the UK, Spain and Italy, found similar differences across Europe where pill usage was higher in

France, Germany and the UK compared to Spain and Italy. A possible explanation for this is given by Spinelli, Talamanca & Lauria (2000), who looked at pill usage in Germany, Denmark, Poland, Spain and Italy who suggest that: "the European countries are in different phases of contraceptive practice: in Northern and Western Europe, use of more modern methods has been stable over the past 10 years, whereas these methods are less common in Southern and Eastern Europe"²⁷. Another explanation for the differences between countries given by Spinelli et al. (2000) is that they: "reflect availability and accessibility, as well as social and cultural attitudes towards fertility control, sexuality, and the roles of women in society".

Another difference between countries in Europe is the age at first intercourse and the age when women start using the pill. Cibula (2008) poses that the use of contraception at first intercourse differ significantly where the rates are highest in Germany and France and lowest in Russia, the Czech Republic and the Baltic states. According to them this in part "reflects the differing quality and impact of sexual education in the countries assessed" (Cibula, 2008). Furthermore there was a difference in the age when women first start using the pill

²⁷ Here has to be noted that this article is somewhat outdated where the dynamics in southern and eastern Europe have changed in such a way that the use of reliable

contraception methods has increased significantly, whilst at the same time pill usage is still relatively low compared to western and northern Europe (Cibula, 2008)

where they start at a younger age in France, Germany and the UK compared to Spain and Italy (Skouby, 2004).

Since fertility is low in almost all European countries, most women must use some form of contraception. Spinelli et al. (2000) and Skouby (2004) point out that in general, women in northern European countries tend to use more reliable methods than women in southern European countries. Furthermore, Cibula (2008) found that in Russia and the Baltic states there is the highest proportion of women who use no contraception or 'other methods' and according to them there is a: "Strong correlation between countries with high economic, educational and health care levels, and a high frequency of awareness and use of more sophisticated methods of contraception such as the IUS". Skouby

further mentions that there is a negative correlation between the use of modern contraception and abortion rates, which is illustrated by the fact that the rise of modern contraceptives across Europe has led to a transition from a culture of abortion to a culture of contraception.

When comparing countries however, it is important to note that country data is always an average of the entire population and, as discussed in the previous paragraph, there may be large differences within countries. To illustrate, in Italy the number of women using modern contraception is much higher in the northern part than in southern Italy (Spinelli et al., 2000) and this indicates that whenever making statements about countries, be aware that you are generalizing and individual woman might not fit the picture portrayed.

6. Final remarks

The aim of this section was to address the effects of the hormonal birth control pill on female life choices, and society. Although it is hard to make any statement without generalizing and disregarding the nuances of the subject we came to the following conclusion: The pill put the fertility decision of its users solely into the hands of women and, although not directly causing a decline in fertility, gave women more power to control their fertility by being far more reliable than

its predecessors, leading to users investing more time in their education and career. Furthermore, admitting pill use is partly determined by social norms and attitudes, at the same time influences these norms and attitudes contributing to the changing role of women in society and societal attitudes towards sexuality and fertility. Finally, despite the fact that pill usages varies greatly between and within countries, depending on religious, social and cultural attitudes

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towards fertility and fertility control, sexuality, gender roles, socio-historical developments, and access to contraception, in general: younger, higher educated, women from a less deprived area and a higher socioeconomic status tend to use the pill more.

The question now is how this conclusion contributes to answering our main research question: To what extent has the birth control pill had a positive influence on women in western societies? To be able to answer that, we need to evaluate whether the impact of the pill has been positive or negative. Although this always depends on your definition of positive and negative impacts, we can make some general statements evaluating the pills impact. For starters empowering women to control their own fertility seems unambiguously positive, as we view anything that promotes equality between men and women as positive²⁸. In addition, the fact that the pill enabled its users to invest more in education and their career is, on the same line of reasoning, viewed by us as positive. The same could be said of the pills influence on social norms and attitudes as these attitudes have shifted to a more equal view of men and women. The unequal distribution across and within western societies is somewhat harder to evaluate. One could say that it is at least not

positive as it is hard to see a positive contribution of having an unequal distribution, unless this promotes equality on other aspects, but this does not seem the case. However, the pill did not cause this unequal distribution since this is due to other underlying factors. Therefore you might reason that these underlying factors have a negative impact, but the introduction of the pill itself did not. Nonetheless, no matter whether you see this unequal distribution as positive, neutral or negative, overall we believe that the balance of the impact of the pill has been largely positive, as in our view, the fact that the pill empowered women and promoted equality for its users and society outweighs its unequal distribution whether this is negative or not.

²⁸ We are aware of our western cultural bias

in making this conclusion.

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Chapter 4 Interdisciplinary approach

To what extent has the combined oral contraceptive pill positively influenced the position of women in western societies?

Key points

- The pill put the fertility decision of its users solely into the hands of women.
- The pill did not directly cause a decline in fertility, but by being far more reliable than its predecessors, the pill gave women more power to control their fertility.
- The reduction of the risk of undesired pregnancy caused by the pill led to its users investing more in their education and career.

In this section we outline and explain our integration of the disciplinary insights. We formulate a common ground, show the framework of our integration and organize the insights of the three disciplines. Subsequently we formulate the hypotheses we based on assembling these insights. This chapter is finished by a conclusion consisting of a reflection, results and a recommendation.

1. Integration

At the start of this study, we set out to answer the question: To what extent has the birth control pill had a positive influence on women in western societies? We have discussed a variety of insights into the effects of the pill on women from three main fields of research: the biomedical studies, behavioral neurosciences and population studies. As regards methodology, there is a strong overlap between the academic scopes that define these fields of research. This resemblance is particularly visible in the epistemologies and experimental nature of the biomedical sciences and the behavioral neurosciences that center on experimental research on the individual scale. Their combined similarity with population studies is smaller, which 'merely' borrows insights from other fields (an exchange that occurs both ways). Population studies centers on insights on the trans-individual scale, which causes the studied phenomena and available methodological tool set to be of a different nature. For the sake of simplicity, here we first define a common ground by approaching our central concept from the three most influential perspectives of biology, psychology and human geography.

Establishing common ground

Central to our evaluation of positive and negative effects of the pill in answering the main research question, is the concept of

human well-being. Most readers will intuitively share a similar idea about well-being - as do the authors of this paper - likely involving some notion of a person's subjective experience of his or her state of affairs. From a strictly disciplinary standpoint, the meaning of the concept 'well-being' is necessarily limited by the ways it can be observed through/applied to phenomena studied in the respective fields of research. This would imply that the definition given above - which is mostly a psychological one - has no explanatory value in disciplines that reject subjective experience as a valid source of information. Only a scholar in psychology can ultimately accept subjective information (i.e. the linguistic contents of human communication) to reflect this.

What then constitutes 'well-being' in those other disciplines? A biologist can state that it is strongly dependent on a person's healthy bodily functioning, and a geographer can point to a certain socioeconomic status, but neither discipline has the linguistic tools (jargon) to define what 'being well' entails. We argue that the concept still has meaning because in these disciplines 'well-being' comes down to an implicit or explicit *assumption* about subjective experience. A biologist may then say that that which psychologists call well-being is empirically well observable in organisms that behave a certain way, albeit indirect. A geographer

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may observe certain societal trends as the cause and/or effect of individuals' well-being, which is again an indirect assessment of the phenomenon. Some may argue that even the psychologist must eventually assume that, in the example of language, the subjective contents of a verbal communication reflect a person's true experience, but this is far less limited than the biologist's mere analysis of the causes and effects of verbal communications.

What is clear from this discussion is that the study of phenomena surrounding women's well-being in relation to pill use requires dealing with methodological differences between each disciplinary approach present in this study. In order to

find out where this is required, in the next section we construct a framework for integration containing the core methodological principles of the three academic scopes defined by the fields of research that contributed to this study. This information has already been discussed in the *In perspective* chapters, so here we remain brief in explanation of the terms.

Integration framework

In our attempt to integrate insights from the (inter-)disciplines dealt with in previous chapters, we deal with a number of important methodological factors to be taken into consideration.

	Biomedical studies	Behavioral neurosciences	Population studies
<i>Epistemology</i>	Empirical observation of biochemical bodily processes in a strictly controlled experimental setting allows for identifying and classification of true causes.	Subjective phenomena can be reduced to physiological processes. These connections can be inferred through empirical experimental methods.	Statistical and demographical data unveil changes, trends, patterns and correlations in the distribution of individual, group and societal characteristics.
<i>Phenomena</i>	Bodily development and functioning, medical pathology	Brain development and functioning, behavior, thought, emotion	Socioeconomic status, education, demographics and user statistics

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<i>Methods</i>	Biochemical experimental research, statistical analysis.	Psycho-physiological experimental research, statistical analysis.	Statistical analysis, geographic analysis questionnaires, interviewing
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Table 1: Oversight of methodological characteristics of the three fields in this study.

The biomedical studies and behavioral neurosciences primarily study phenomena in a controlled laboratory setting, both making attempts at uncovering *law like* or *causal relations*. The information that is gathered through these experiments can therefore be called *normative*. In biomedical experiments these relations are sought between *empirically observable* events. In the behavioral neurosciences experimental research is extended to include *subjective* phenomena, to find such relations between psychological phenomena and their biological causes (psychophysiological). Both these approaches can be regarded *bottom-up*, as general human functioning is researched in a modular fashion, by focusing on isolated processes as part of a complex system. Putting a strong focus on uncovering small, isolated causal relations through experimental testing in a laboratory environment does limit the ability to make normative statements about reality, as the complexity of any studied phenomenon outside the lab is greatly enhanced by a real-life, uncontrolled environment.

The approach in population studies in contrast can be called *top-down*, gathering *descriptive* knowledge through analysis of large-scale societal trends. It makes much more use of *correlational* research where data which might not have been gathered for that specific research is analyzed to find correlations between different factors. The underlying causal relations, if present at all, are usually subsequently *inferred* (i.e. based on the normative sciences) by the researcher. The limit of this approach is that, although almost all phenomena can be studied, there arises an increasing amount of uncertainty about causal relations as these cannot be isolated and uncovered in a controlled environment, leaving room for speculation and error in the *interpretation* of the researcher.

In this study we apply insights from the normative sciences to the correlational data from the descriptive sciences, in order to make causal statements about phenomena we otherwise could not. To remove one of these approaches would invalidate any further conclusions, stressing the interdisciplinary nature of this research.

Organized insights

Biomedical studies

- The pill suppresses and influences natural estradiol and progesterone levels with synthetic compounds
- The pill can induce many adverse effects, like every medicine
- The pill affects the immune system and increases risk of inflammatory disease
- The pill has some non-contraceptive health benefits
- Newer generations of the pill are less harmful
- Effects of long-term use are not well known yet

Behavioral neurosciences

- The pill alters females' brains and behaviors indirectly (through suppression of natural sex-hormones) and directly
- Pill influence on the brain is clearly present but remains to be further classified, studies on behavioral effects are inconsistent and produce mixed results
- Pill effects have been found on aspects of memory, language and visual processing
- Pill use can negatively influence mood and stress responses
- Pill use influences sexual and mating preferences

Population studies

- The pill put the fertility decision solely into the hands of women
- The pill influenced and interacted with the changing role of women and societal attitudes towards sexuality and fertility
- Pill usage rates vary greatly between and within countries
- Pill use is relatively larger in younger women and rises with:
 - Education level
 - Socioeconomic status

Formulating Hypotheses

Integrating the insights listed above, we formulated a set of hypotheses. These hypotheses have been constructed through extrapolation of the insights garnered from the normative biomedical studies and behavioral neurosciences, and the predominantly descriptive population studies. These hypotheses all require future research, and are accompanied by some of our thoughts on how to advance from there.

First, combining insights from the normative biomedical and behavioral neurosciences alone, we propose the first three hypotheses:

1. *The pill has considerable long-term effects on women's bodies and brains.*

This is especially important for women who start using the pill at a relatively young age. Pill use affects natural hormone levels that have an important function the development of the female body and brain. Although a small number studies have shown long-term effects on the physiological level to occur, much of its effects remain uninvestigated. Long-term investigations into effects of the pill on bodily and brain functioning - including associated health risks - should be conducted to elucidate these effects.

2. *The pill negatively influences women's physical and mental health.* The pill

increases the risk of inflammatory diseases, can negatively affect mood, and may even cause depressions in some women. In North-European societies, where depression rates and pill-use are relatively high, such a factor should be further researched

3. *The pill's effects on women's mate preferences can negatively impact genetic diversity in future generations.* As the pill biologically causes women to prefer genetically more similar men, this can negatively affect genetic diversity in their offspring. This in turn is associated with greater risk of health complications, not directly for users, but instead affecting future generations. Investigation in high and low pill-use countries spanning over multiple generations is required to see how this affects future generations.

Widening the scope to include of the descriptive insights on the societal level, we here add insights from population studies to arrive at the next three hypotheses:

4. *The pill changes women's partner selection through changes in biological systems and socioeconomic factors.* As mentioned, the pill directly affects sexual preferences in women through biological changes in the body and brain. This change in partner selection also seems to occur indirectly, as the availability of the pill

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provided women with greater freedom to engage in sexual activities, at a minimum risk of unplanned pregnancy. This results in the ability to invest time and resources in education, which increased women's incomes and social mobility. It also removed the financial necessity to find a caretaking partner, further freeing up life and mating choices. It will be interesting to further investigate whether non-pill users that have reached similar socioeconomic positions behave similarly with regard to partner selection, to see what the respective effects of biochemistry and society are.

5. *The pill positively affects women's career opportunities.* Women's increased control over family planning matters made the pursuit of getting education and building a career a safer (uninterrupted) investment. The effects of the pill on women's brains and thinking are not yet well understood, and there is no saying how this affects women's functioning in a professional context. Nevertheless, women in high pill-use societies have generally grown into more powerful and stronger socioeconomic positions, which forcefully changed societal preconceptions, amongst others resulting in increased presence and acceptance of women in high-dedication workplaces. It remains to be seen whether this change continues in a future where pill-use no longer increases as strongly as previously, as

societal changes are generally slower than effects on the individual.

6. *The pill affects women's relationships at later ages.* Greater financial independence removes the necessity to stay with a partner who provides income. With minimized risk of pregnancy, temporarily staying with a partner became more feasible. As stopping pill use can change women's sexual satisfaction in a relationship, this might for example have led to higher rates of cheating. Effects of the pill on health generally come at later age, such as the development of cancer. Having a disease influences lifestyle, possibilities of action, and thus interaction. These and other changes in relationship dynamics make it worth investigation whether increased pill use in countries has accompanied increases in divorce rates.

With regard to the positive effects on social level, it is important that women are very well informed about the pill. This may prevent discontinuation of use, because of fear of risks or dissatisfaction about side effects. Compliance is a prerequisite for the protective effect of the pill that induces independency.

Additionally, all the hypothesized effects are thought to affect certain people more than others, as we gathered from insights provided the population studies:

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7. The pill's associated health risks disproportionately affect women (1) at a younger age, (2) from higher social classes and (3) with higher education levels. Pill use is relatively high among post-adolescent users, and declines at later ages. Furthermore, pill use rises both with social class as well as with education levels. Further investigation into demographics and health statistics could point out whether these groups are indeed more vulnerable to associated health risks.

2. Conclusion

In this study, we sought to provide insight into what have been the effects of the birth control pill on the well-being of women. We focused on European countries, in part because these are among the societies where pill use is highest. We conducted literature reviews in the fields of biomedical sciences, behavioral neuro-sciences and population studies, and in that process have built up the disciplinary expertise required to advance our knowledge for our main research topic:

To what extent has the birth control pill had a positive influence on women in western societies?

8. The pill's effects on population health and society dynamics will be most visible in northern and western European societies.

On average, women from southern and eastern European countries tend to use the pill less, and as such they are - for example - at lower risk of mental or physical health issues compared to women in northern and western Europe. It is hard to point out whether increases in pill use would be the cause or effect of certain societal trends, but researching trends in societies where other female contraceptive methods are high in prevalence should provide more insight.

Reflection

Integrating our disciplinary insights presented us with a number of challenges. The first challenge was how to combine the normative and descriptive knowledge from the different fields, and creating a frame-work that facilitated the creation of new insights about their combined values. Both biomedical sciences and behavioral neuro-sciences use experimental research with the aim of uncovering natural causes. This limits the phenomena to be studied to those that can be controlled in a laboratory. Population studies does not use a laboratory environment, enabling it to widen the scope of phenomena that can be studied. The downside of this is that no claims about

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causality can be made, and conclusions are largely drawn from correlational data and statistical probability. Establishing a common ground presented us with another challenge, as the conception of a 'positive effect' is eventually in the eye of the beholder. This meant in part that we had to bridge the domain of subjective experience with objectively observed phenomena. A common ground allowed us to set up a framework for integration, enabling us to combine correlational data with knowledge on causal relations. It then enabled us to form hypotheses about the underlying causes of real-world phenomena.

Results

The causal relations gleaned from the fields of biomedical sciences and behavioral neurosciences also caused us to reevaluate inferences drawn from the correlational statistics, sometimes leading to the plausibility of hypotheses which at first could not be explained. For instance: population statistics shows that the use of the pill is correlated with better health. In controlled experimental settings the pill has shown many negative effects increasing the risk of inflammatory diseases. On the other hand these risks may be relativized with statistics. The pill has shown to mainly negatively affecting women's mental health.

This leads to the conclusion that pill use is not a direct cause for better health, but rather

that the correlation between good health and pill use is results from the disproportionate prevalence of certain characteristics in women that use the pill, such as their better health overall.

This is consistent with another insight from the population studies: Pill use is not distributed equally among western societies. Younger women, women who are higher educated, and/or are from less deprived areas in western and northern Europe are therefore at greater risk of experiencing the negative side effects of the pill. However, compared to women of older age, women who are less educated, or women who come from more deprived areas in eastern and southern Europe, these women are also generally healthier.

Concerning societal effects in a broad sense, the effects of the pill are mostly positive, driving a more liberal societal attitude towards sexuality, childbearing and women's career ambitions. These trends affect users and non-users alike, and few will argue that the increased freedom of women to choose their life paths is essentially not a good thing. There are some who will condemn the pill's influence on females' mating preferences and sexual behaviors, on cultural grounds that regard these altered behaviors as unnatural and therefore bad. From a biological and population health standpoint, women preferring genetically more similar men is a factor that should be

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carefully monitored. Not so much for users themselves, but for future generations, as genetic diversity is in everybody's interest.

Because the exact effects of the pill are very complicated and sufficient research is not always available, especially concerning the effects on behavior and inflammation processes, we have taken caution in formulating a conclusion in the form of possible and expected effects. Although many results are mixed and often inconclusive, we conclude that on the mental and physical health level the pill has brought certain negative effects for its users, but these can be considered small. However, as consequences can be dire for some users it is still an important factor to take into account. The pill has meant such an

improvement for women to be able advance their education, grow their incomes and acquire greater social mobility, that these positive effects seem to easily outweigh all negative aspects, but with the general lack of long-term medical and bio-behavioral research, there is still enough unknown to maintain a careful approach to this greatest of hormonal experiments ever conducted.

Recommendation

Future studies may involve more long-term research on large cohorts. The large differences caused by the pill on the physiological need to be studied more thoroughly. Thereby it may be of social interest to have our findings examined by an ethicist, to 'translate'

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