COMBINED ORAL CONTRACEPTIVES

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INTRODUCTION

Combined oral contraceptives (COCs) are the most used hormonal method of contraceptives worldwide (Brynhildsen, 2014). They contain artificial doses of estrogen and progestogen and became available in the early 1960s in most western countries (Craik J., Melvin L., 2015).

The first generation of combined oral contraceptives was launched to the public after clinical trials were carried by pharmaceutical companies from several countries in the sixties (Dhont, 2010; Davtyan, 2012).

The second generation was introduced in the early 1970s. Combined oral contraception based on levonorgestrel and norgestrel were the most prescribed, using new types of progestins and estrogen combinations to improve the COCs. The hormonal dosages were reduced due to health problems and side effects that they had been causing such as weight gain and mood disturbances (Brynhildsen, 2014). Consequently, the new combined oral contraceptives caused fewer side effects and the aura of fear surrounding the use of these pills was diminished, increasing the sales of this product (Dhont, 2010; Davtyan, 2012).

The third generation was produced after researching levonorgestrel derivates such as desogestrel and gestodene. It was a combination of these two progestins with ethinylestradiol. However, in the late nineties, studies revealed a high risk of venous thromboembolism, associated with these COCs (Dhont, 2010; Davtyan, 2012).

The fourth generation of COCs is the most recent one and it has been developed to reduce the side effects and potential health problems. New progesterone called drospirenone was introduced along with several new types of estrogens such as estradiol (Dhont, 2010; Davtyan, 2012).

Course of action

The combined oral contraceptives prevent ovulation by suppressing the luteinising hormone and follicle-stimulating hormone. Progesterone regulates processes required for reproduction. These hormones can fluctuate to such an extent in the blood from one ovarian phase to the next that, depending on the dose administered, it can cause the inhibition of pregnancy or enhance it (H. B. Croxatto, 2005).

Progestogens and estrogen are steroids that modify clotting factors and allow changes to the endometrium, tubal motility, and cervical mucus thickness (affecting sperm activity) which contribute to the contraceptive effect. (Faculty of Sexual and Reproductive Healthcare, 2011).

The regimen includes 21 days of taking estrogen and progestogen pills. The first seven days are focused on ovulation inhibition and the 14 days left revolve around maintenance. The hormone-free interval lasts seven days and during this period no pill or a placebo pill is taken. This simulates the natural menstrual cycle, tending to induce lighter bleeding than normal (Craik J., Melvin L., 2015). The use of COCs can decrease menstrual pain and heavy menstrual bleeding. In addition, they can also reduce acne vulgaris (Faculty of Sexual and Reproductive Healthcare, 2011).

CARDIOVASCULAR DISEASES

Estrogen and progesterone are located throughout the body but are produced in the ovaries. The cardiovascular system has some pathways that activate the receptors of these two hormones on endothelial and myocardial cells.

Estrogen receptors modulate vasodilatation, endothelial cell growth, and smooth muscle cell proliferation, and in addition, they reduce cholesterol LDL. This hormone has an impact on the cardiovascular system by influencing risk factors like the lipid profile using the genomic pathway. The alteration depends on the estrogen dose and the delivery route (Shufelt & Bairey Merz, 2009).

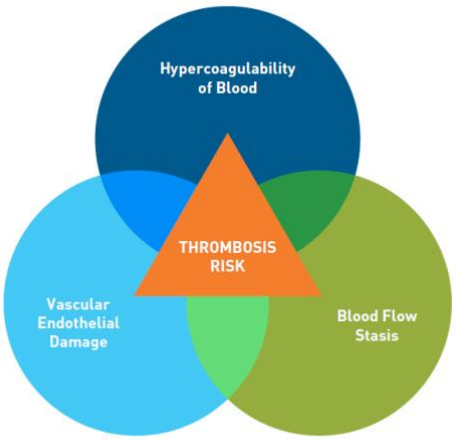
The role that progesterone plays in the cardiovascular system is less understood. The contraceptive hormones inhibit ovarian androgens, decreasing plasma testosterone. This condition is beneficial to women with polycystic ovary syndrome but correlates with a higher cardiovascular risk (D.A. Ehrmann, 2005).

Venous Thromboembolism

Venous thromboembolism (VTE) caused a wave of fear in the media regarding the link between the oral contraceptive pill and cardiovascular diseases in the late 1990s. The impact this disease has on cardiovascular health is one of the main reasons why some women prefer other contraceptive methods.

Venous Thromboembolism occurs when a blood clot formed by tissue damage blocks the blood flow and oxygen in a vein, creating a thrombus. (National Heart, Lung, and Blood Institute, 2021). Several factors increase the thrombotic risk such as natural anticoagulants or abnormalities in coagulation factors (see figure 2). Fibrinogen is one of the twelve clotting factors involved in the stabilization of the clot and platelet aggregation. It is formed by the factor thrombin and estrogen encourages its formation.

FIGURE 2. Virchow's Triad[10]



Adapted from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I9-I16. doi: 10.1161/01.CIR.0000078469.07362.E6.

(Anderson & Spencer, 2003) Figure 2.

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are the two main types of venous thromboembolism. DVT takes place in the large veins of the pelvis or the legs and PE occurs when a blood clot detaches from the vein wall and travels through the body to the pulmonary arteries (Haley M.Phillippe, 2017).

The correlation between combined oral contraceptives and the increase of the risk of venous thrombosis has been well established for more than 20 years (Kemmeren et al., 2001). The COCs influence haemostasis by increasing coagulation and clotting factors. As they stimulate the formation of thrombin and fibrin, the risk of VTE is higher. The use of progestin-only oral contraceptives has not presented a significantly increased risk of venous thromboembolism, making them less harmful for women with cardiovascular health problems (Blanco-Molina et al., 2012).

A meta-analysis done with 25 studies concluded that all COCs increase the risk of venous thrombosis. Third-generation oral contraceptives show a significant growth of the risk compared to second-generation users (de Bastos et al., 2014).

Ischemic stroke

An ischemic stroke occurs when the oxygen and blood flow to the brain are temporarily blocked by a blood clot. Fatty acids can cause a partial blockage and consequently, the reduced blood flow causes cells to die, damaging the brain permanently (NHS, 2021). More than 80% of stroke cases are acute ischemic strokes, which have a death rate of 41.6% and, if survived, could require aftercare assistance. (Moskowitz, Lo and Iadecola, 2010).

The COCs are associated with a higher risk of stroke. Estrogen plays a big role in thrombogenic changes and influences coagulation factors which could cause vascular lesions and the formation of thrombi, triggering a stroke. Combined oral contraceptives with a higher dose of ethinylestradiol have been shown to increase the likelihood of a stroke by 2.7 times more than other COCs (Lima et al., 2017).

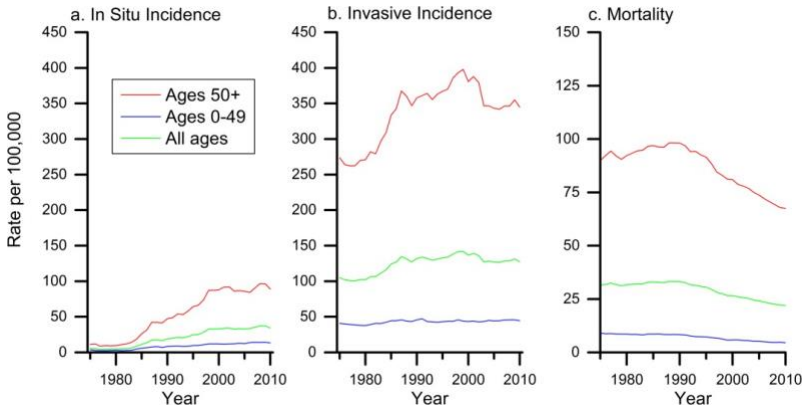
CANCER

Combined oral contraceptives are used daily by millions of women in the world (Brynhildsen, 2014). However, misunderstandings and myths promoted by the media and a lack of information have left women wondering if it increases the risk of cancer. These concerns were similar to the ones caused by the second generation of COCs, as previously mentioned.

The Royal College of General Practitioners Oral Contraception Study presented one of the biggest studies in the field, which follows 46000 women over 44 years. It concluded that the risk of developing colorectal, ovarian, lymphatic, hematopoietic, and endometrial cancer is decreased for more than 35 years after the COCs have ceased to be taken.

Breast cancer

Breast cancer is formed in the cells of the breast. Depending on where cancer has developed, it can be non-invasive (in situ) or invasive breast cancer. The non-invasive is located only in the ducts of the breast. Invasive cancer is the most common type, and it develops when cancer has spread to the surrounding breast tissue (NHS, 2019). This disease affects 1 in 8 women. The likelihood that cancer will develop in the next 10 years increases with age, and therefore women over 50 are much more vulnerable than other age groups. (Desantis et al., 2013)



(Carol Desantis et al., 2013 figure 1). Incidence and Mortality Rates of Female Breast Cancer by Age, United States, 1975 to 2010. Rates are age adjusted to the 2000 US standard population within each age group. Sources: Incidence: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 registries, 1975-2010. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences; 2013; data were adjusted for reporting delay. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the SEER program.

Hormonal factors are involved in the development of cancer. For this reason, several studies have researched the correlation between oral contraceptive use and this disease.

It was observed that the increased risk of developing breast cancer in women who were over 55 years old, and users of combined oral contraceptives was not statistically significant. Women in the highest category of the duration of oral contraceptive use had the highest risk associated with breast cancer, but it was nonsignificant (Van Hoften et al., 2000). Another study reported an increased risk of developing breast cancer in recent users of the COCs, but this risk was lost five years after stopping the use of the combined oral contraceptives (Iversen et al., 2017).

Cervical cancer

Cervical cancer is the term for any cancer located in and around the cervix. 99% of cases are caused by the human papillomavirus (HPV) (WHO, 2020), but the use of COCs is one other factor that can cause this disease. Globally, it is the second most common cancer in women, after breast cancer (Organization, 2015). Mortality rates have decreased considerably with advances in screening diagnosis and treatment, and consequently most deaths are in low-income countries (Moore, 2006). The use of combined oral contraceptives has drawn attention to the possibility that this may be a risk factor for developing cervical cancer.

A comprehensive systematic review along with meta-analysis showed a positive correlation between the use of COCs and cervical cancer (Faculty of Sexual & Reproductive Healthcare, 2011). This was associated with adenocarcinoma, which can be caused by the hyperplasia of the endometrium that the combined oral contraceptives can induce due to the hormonal imbalance (National Cancer Institute, 2018). The longer a woman has taken the COCs, the higher risk she has of developing this type of cancer. The HPV status was insignificant in these results (Gierisch et al., 2013). This conclusion is consistent with previous studies and analyses (Asthana, Busa and Labani, 2020).

Endometrial cancer

Endometrial cancer is a disease located in the endometrium cells. If this cancer is not diagnosed early and is able to spread, it can cause cervical cancer due to its proximity. It is also linked to obesity and the resulting hyperinsulinemia and so a healthy and balanced lifestyle can decrease the risk of developing this type of cancer (Moore and Brewer, 2017). Most women who suffer from this disease are over the age of 45, the overall age is 60 (American Cancer Society, 2021).

It has been observed that COC users have a lower tendency to develop endometrial cancer than other women. In this case, the fluctuation of the risk is inversely proportional, as the longer the woman has taken the contraceptives, the lower the risk of developing endometrial cancer is. This falls every five years and after 10 years is reduced to nearly zero in most women. (Collaborative Group on Epidemiological Studies on Endometrial Cancer, 2015).

Ovarian cancer

Ovarian cancer is very rare but has a high mortality, as it is usually diagnosed at late stages. It happens when cells in the ovaries grow out of control, and it can spread to other parts of the reproductive system like the fallopian tubes. There are three main types of ovarian tumours, and they are usually linked to age. Epithelial cell tumours are the most common; germ cell tumours are typical in younger patients, and stromal cell tumours affect the tissue that produces estrogen and progesterone (American Cancer Society, 2021) (Roett MA, Evans P., 2009).

The use of combined oral contraceptives increases protection against ovarian cancer because the COCs provide a reduced unopposed estrogen environment and avoid the formation of ovarian carcinogenic cells. Combined oral contraceptives are often prescribed for women with endometriosis, and it is known as the only chemopreventive factor against ovarian cancer. The longer the use, the lower the risk of developing this disease (Modugno et al., 2004).

CONCLUSION

Combined oral contraceptives have an impact on the health of women all around the world. While they increase the risk of venous thromboembolism and stroke, only cervical cancer has a positive correlation with COCs. The association between breast, endometrial and ovarian cancer and COCs is not statistically significant. Moreover, the longer the use of combined oral contraceptives, the higher protection they provide against endometrial and ovarian cancer.