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Review Article

Hormonal Contraceptives

The effects of Hormonal contraceptives on the various biomarkers levels: A review

Fallah S.[1*], Sanjary M.[2]

DOI:

[1*] Soudabeh Fallah, Department of Biochemistry , Iran University of Medical Sciences, Tehran, Iran.

[2] Maryam Sanjary, Research Center of the child infectious diseases of Rassole Akram of Iran University of Medical Sciences, Iran.

Combined Oral Contraceptions (COCs) is widely used as an effective and reliable method for pregnancy prevention, as well as for other important noncontraceptive reasons, including reducing menstrual pain and cramping,reducing heavy bleeding or menorrhagia, normalizing irregular periods and treating pelvic pain associated with endometriosis, among others. As the evidence of COCs impacts on some biochemical biomarkers related to diseases such as cardiovascular disease, diabetes, systemic high blood pressure, inflammatory disease, stroke, cancer etc. is inconclusive, contradictory and limited by methodological inconsistencies, we did a systematic review, searching on PubMed and Embase, aiming to investigate the possibility of an association between consumption of the various forms of hormonal contraception and biomarkers levels alteration and also to identify, collate and critically appraise studies assessing the influence of hormonal contraceptives on these diseases spectrum and expose available scientific evidence to create individualized plans to prescribe oral contraceptives for patients based on their needs, lifestyles, co morbidities, and reproductive plans.

Keywords: Hormonal Contraceptives, Biochemical biomarkers, Inflammatory diseases, Cancer, Heart disease

Corresponding Author

Soudabeh Fallah, , Department of Biochemistry , Iran University of Medical Sciences, Tehran, , Iran.

Email: fallah.s@iums.ac.ir

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Introduction

Hormonal contraceptives are available in various dosage forms (Table1) [1] and for different routes of administration: oral, intramuscular, vaginal, transdermal, subdermal implants and associated with the intrauterine system [2]. Their mechanism of action is to block ovulation by inhibiting the secretion of follicle stimulating and luteinizing hormone; they thicken the cervical mucus, which makes it difficult for the sperm to pass and cause the endometrium to be unreceptive to implantation [3]. As we know, COCs is widely used as an effective and reliable method for pregnancy prevention, as well as for other important no contraceptive reasons, including reducing menstrual pain and cramping, reducing heavy bleeding or menorrhagia, normalizing irregular periods and treating pelvic pain associated with endometriosis, among others [4]. The controversial data are available regarding the risks and benefits of contraceptives consumption and HRT and diseases. So we did a systematic review, searching on PubMed and Embase, aiming to investigate the possibility of an association between the various forms of hormonal contraception taking and biomarkers levels alteration and also to identify, compare and critically estimate studies assessing the influence of hormonal contraceptives on the diseases spectrum and expose available scientific evidence for create individualized plans to prescribe oral contraceptives for patients based on their needs, lifestyles, co morbidities, and reproductive plans. We identified many relevant prospective studies, the most of these studies, but not all, showed a significant association between COCs consumption and some biochemical marker levels changes, contradictorily. The investigated biomarkers consisted of: Antioxidant factors, cardiovascular diseases markers and inflammatory markers. It is noteworthy that effect of the contraceptives consumption on the other parameters such as Obesity, cancer, lipid profile, FBS, BP, BMI and etc. has also investigated. In this systematic review, the results of the relevant studies would be compared and provide a comprehensive discussion and resolve contradictions.

There is no generally accepted way to classify combined oral contraceptives according to generations of progestogens.

The most common classification system was used, which is in line with biological properties per group and is reflected in their effects on levels of sex hormone binding globulin.

Classification of hormonal contraceptive

Usually, COC classification includes estrogen dose or molecule, type of progestin and route of administration. While the first pills contained high doses of synthetic estrogen (150 mg of ethinylestradiol or mestranol), current COCs now deliver 50 to 15 mg per day of ethinylestradiol. New formulations delivering natural estradiol (E2) have recently been marketed. A quadriphasic COC combining E2 valerate and dienogest has recently been approved in Europe and the USA, and a second monophasic COC that combines E2 with nomegestrol acetate, a progesterone-derived progestin, is now available in several European countries. COCs can also be classified into generations (first, second, third and other) depending upon the type of progestin and their introduction into market. The so-called first generation pills that contained either norethisterone acetate, lynestrenol, ethnodiol acetate or norethynodrel are currently no longer used [5]. COCs also include non orally administered drugs, such as the combined ethinyl-estradiol/norelgestromin transdermal patch and ethinylestradiol/etonogestrel vaginal ring. These two new methods provide continuous hormone dosing and simplify obedient.

The presently available oral contraceptives are both second and third generation pills; second generation pills containing norgestrel or levonorgestrel, and third generation containing desogestrel, norgestimate or gestodene. Pills with other type of progestins are classified as other generation pills and contain either progesterone or testosterone-derived progestins including cyproterone acetate, drospirenone, dienogest, chlormadinone acetate or nomegestrol acetate. Drospirenone, an aldosterone antagonist, and cyproterone acetate are molecules introducing high anti androgenic effects. Using progestin only products as a contraceptive method may be an attractive option for women with contraindications for the consumption of COCs. Four types of progestin only contraceptives are currently available in Europe and in the United States:

-Progestin only pill that deliver low daily doses of progestin (norethindrone, levonorgestrel or desogestrel)

- Injectable 3 month contraceptives (depot medroxyprogesterone acetate DMPA) administered Intramuscularly

- Levonorgestrel implant or more recently etonogestrel single-rod implant which provides effective contraception for three years

- Intrauterine device containing levonorgestrel, effective for five years [6].

Via a network meta-analysis for COCs classification by Bernardine et al [7] the following progestogens were also classified as first generation; lynestrenol and norethisterone. Norgestrel and levonorgestrel were categorised as second generation progestogens; and desogestrel, gestodene, and norgestimate were classified as third generation progestogens. This classification was irrespective of ethinylestradiol dose.

Publications reporting on generations according to another classification were included. To assess the influence of combining different classifications, an analysis restricted to studies using the above described classification was performed. Many different combined oral contraceptives are available. 10 frequently prescribed oral contraceptives for the network meta-analysis were selected:

- 20 μg ethinylestradiol with levonorgestrel (20LNG)
- 30 μg ethinylestradiol with levonorgestrel (30LNG)

50 μg ethinylestradiol with levonorgestrel (50LNG)

- 20 μg ethinylestradiol with gestodene (20GSD)
- 30 μg ethinylestradiol with gestodene (30GSD)
- 20 μg ethinylestradiol with desogestrel (20DSG)
- 30 μg ethinylestradiol with desogestrel (30DSG)
- 35 μg ethinylestradiol with norgestimate (35NRG)
- 35 μg ethinylestradiol with cyproterone acetate (35CPA)
- 30 μg ethinylestradiol with drospirenone (30DRSP)

The 20LNG, 30LNG, and 50LNG were categorised as second generation progestogens, and 20GSD, 30GSD, 20DSG, 30DSG, and 35NRG were calssified as third generation progestogens. 35CPA and 30DRSP were not used in this classification by generations [7].

In other category, combined oral contraceptives have only one strogen, ethinyl estradiol (EE), in various doses formulated with a progestin. Progestins can be grouped chronologically. First generation progestins, commonly referred to as estranges include norethindrone acetate and ethynodiol diacetate. Second generation progestins, called gonanes, are more potent and norgentral and levonorgestrel (LNG). Third generation progestins also called gonanes have reduced androgenic and metabolic effects and include novestimate desogestrel and gestodene (not available in the united state). Finally a newer miscellaneous category in the form of: drospirenone an antimineralocorticoide with progestogen and antiandrogenic activity was introduced [8]. In other formulation oral contraceptive pills come in two types of formulations. In monophasic oral contraception, all the "active"

Pills contain the same amount of ethinyl estradiol and progestin (traditional pack: 21 days active/7 days

Placebo). The 'active' pills in triphasic formulations vary in the amount of ethinyl estradiol and/or the

Progestin (traditional pack: 21 days active/7 days placebo). Some newer formulations of extended

Monophasic forumulations include cycles of 84 active pills/7 days placebo or 24 active pills/4 days placebo.

Use of Oral Contraceptives in Women with Migraine

Susan Hutchinson, MD

Family Medicine, Women's Medical Group of Irvine, Irvine, CA

American Headache Society • 19 Mantua Road, Mt. Royal, NJ, 08061 • 856.423.0043 • www.AmericanHeadacheSociety.org

COCs and Antioxidants alterations:

Antioxidant Enzymes

The pool data of the study about the effect of low dose contraceptive pills (LD) OCPs on the activities of the erythrocyte antioxidant enzymes glutathione peroxidase (GPX) and superoxide dismutase (SOD) of OCP consumers in our previous study [9] identified that erythrocyte GPX activity in OCP was significantly higher than controls but the same comparison for SOD activity between control group

And women receiving OCPs showed an no significant (−2%, p=.699) decrease. We showed that duration of the OCPs intake beyond 36 months had an effect on the magnitude of the increase (+16.2%) and the decrease (−11%) in GPx and SOD activities, respectively. A significant and considerable (no significant) correlation was also found between GPx and SOD activities with the duration of OCP consumption, respectively. It was suggested that OCPs may stimulate or reduce the activities of GPx and SOD enzymes, respectively. This may be due to an effect of these pills on bone marrow erythroblast maturation via stimulation or inhibition of the synthesis of new active GPx and SOD molecules or may be a result of the increased frequency of an allele of the GPx and SOD enzymes .These alterations in GPx and SOD activities may be related to their probable protective effects in response to various physiological or pathological properties of OCPs. It seems that probably free radicals produced during metabolism of OCPs provoke the activities of antioxidant enzymes. We also found that OCP intake resulted in a significant decrease in serum zinc levels ($p \leq .009, t = -3.666$) and an alteration of selenium levels but no significantly ($p = .08, t = 0.935$). We found that duration of use beyond 3 months had no effect on the magnitude of the decrease in serum zinc levels [10]. In a study performed by Massafra C. [11], antioxidant erythrocyte enzyme activities during oral contraception be investigated and their findings clearly suggest that the use of combined oral contraceptives leads to an increase in Mineral and trace elements.

In a cross-sectional study [12] the relationship between contraceptive consumption and trace elements (serum zinc, selenium, phosphorus and magnesium) levels was investigated, and a reduced levels of trace elements in women under study was found. It is noteworthy that relevant reduction is proportional to the duration of contraceptive use. The achieved results of the oral contraception pill containing ethinylestradiol and drospirenone effects on oxidative stress in women 18-35 years old showed that introduced combination of ethinylestradiol and drospirenone induces the heightening of lipid peroxidation correlated with high levels of copper, a situation that could be associated with increased cardiovascular risk [13]. The Effect of different contraceptive methods on the oxidative stress status of women aged 40 48 years from the ELAN study in the province of Liege, Belgium was investigated. It was concluded that intake of OC significantly increases the lipid peroxidation in women aged 40-48 years. This may represent the OC as a potential cardiovascular risk factor for these women [14]. In a prospective case-control study the serum zinc status of rural women taking combined OC are examined. Their mean serum zinc of women taking OC was reduced significantly in comparison with controls ($p<0.001$) [15-16]. Antioxidants, in particular carotenoids, may influence the risk for cardiovascular disease. In a study by Berg G. et al. [17] the influence of oral contraceptives (OC) on the serum concentration of beta-carotene, which may in turn affect the risk of cardiovascular diseases due to its antioxidative impact was investigated. A negative association was found between OC taking and serum beta-carotene concentration via bi- and multivariable analyses, after adjustment for age, smoking, alcohol consumption, dietary intake of beta-carotene, use of vitamin supplements, body mass index, pregnancies, and total triglyceride and cholesterol levels. A strong interaction was observed between OC use and age on beta-carotene concentration. While no relationship was seen between OC taking and serum beta-carotene in the youngest age-group (18-24 years), there was a modest but significant negative association between OC use and beta-carotene levels among 25-34 years old women. It was identified that OC consumption was associated with a strong decrease in beta-carotene levels among 35-44 years old women. The interaction between OC use and age could partly be explained by age dependent OC taking with higher estrogen content [16]. Changes in metabolic processes and trace element profiles are governed by genetic disposition as well as environmental factors. Alterations in lifestyle, dietary habits environmental factors, and active ingredients of hormonal agents have been known to affect status of micronutrients in humans. Some of these micronutrients eg. manganese, vitamin B12 and magnesium are co-factors and co-enzymes which are involved in important metabolic pathways. Changes in the tissue level or bioavailability of these elements could play a significant role in health risk and the pathogenesis of some disorders such as cardiovascular complications; the aging process and certain cancers have been associated with the contraceptives use. Some of these trace elements for example, selenium and manganese are potent

Antioxidants known to be involved in preventing free-radical induced damage. These antioxidants are involved in preventing the formation of free radicals induced damage, preventing the formation of radicals, scavenging them or promoting free radical decomposition in the body. Zinc and copper have been shown to raise immune response and their importance in the malnourished persons has been documented. Disruption in the blood levels of these trace elements could be an important health risk. Possible changes in serum trace elements and vitamins of women on contraceptives have been suggested. For instance It has been shown that contraceptives (compounds with oestrogen-progestrogen-like actions) have been used by women in Nigeria to control fertility to interfere with the absorption of some micronutrients such as trace elements and vitamins. The relationship between contraceptive use and trace elements in a cross-sectional randomized study was investigated. The study conducted on total of 100 women of child-bearing age on different contraceptive methods: 50 on oral contraceptives, 25 on injectables and another 25 on intra-uterine device. The mean serum zinc, selenium, phosphorus and magnesium levels obtained from subjects on contraceptives were significantly lower ($p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.05$ respectively) than those of the control group. However, the mean serum copper iron, calcium and cadmium levels were significantly higher ($p < 0.05$) in participants on contraceptive when compared with the control group. Manganese and lead levels were similar in participants and control groups. A significant association was fond between some trace elements and the duration of contraception and body mass index of the participants [17].

A meta-analysis was designed by Babic Z. et al. [18] through a systematic literature overview and quantitative data analysis to establish the range of Cu increase in OC users compared to nonusers. The results showed that increase in Cu level exponentially decreased in COC users over time, with a rapid decline through the 1960s and 1970s. After controlling for the publication year, use of COC increases the mean serum/plasma Cu level by 0.57 mg/L (95% confidence interval 0.49-0.66 mg/L). They showed that COCs commonly raise serum Cu to levels between 1.5 and 2 mg/L, which are above reference levels. Although these levels are not considered toxic, there were suggestions

That such Cu increase could be implicated in oxidative pathophysiological processes in the body. Further research on safety of COCs use, including oxidative-stress-related effects, was warranted.

High serum copper concentration in women using oral contraceptives is well known. In a bi- and multivariable linear regression models with log-transformed it was shown that oral contraceptives consumption was positively associated with copper levels. The amount of copper was introduced as dependent variable whereas the oral contraceptive preparations and potential confounding variables were introduced as independent variables. It was shown that copper levels in women using oral contraceptives varied more strongly by different progestin compounds than by estrogen contents. Although increased serum copper concentration was found in users of all types of oral contraceptives, but this increase was more impressive among women taking oral contraceptives with antiandrogen effective progestins like antiandrogens or third generation oral contraceptives containing desogestrel. The highest increase of serum copper was seen in women using oral contraceptives containing antiandrogen progestins (55%; 95% CI: 37-76%), followed by desogestrel (46%; 95% CI: 36-56%), norethisteron/lynestrenol (42%; 95% CI: 29-57%), and levonorgestrel (34%; 95% CI: 24-45%) [19]. In prior study the serum copper and zinc levels of combined estrogen-progestogen contraceptives users and users of injectable progestogen were investigated. Consumption of combined estrogen-progestogen contraceptives resulted in a significant decline in serum zinc levels within 3 days and an increase in serum copper levels within 10 days. It was observed that amplitude and occurrence time of zinc levels decrease and copper levels increase were not changed by chemical composition, dosage, administration route and duration of use beyond 3 month in combined estrogen-progestogen contraceptives users. A significant decline was found in zinc levels within 24 hours after injection of progestogen (norethindrone enanthate, 20 mg/month) while serum copper concentration was not changed. In case of injectable progestogen the type of drug, dosage and duration of taking beyond 1si month had no effect on the magnitude of the decrease in serum zinc levels [20].

A study designed by Prema et al to investigate the association of the long-term

Use of a copper intrauterine device (IUD) with any change of the serum copper concentration and thereby whether the copper absorption from the device in utero could result in copper toxicity. No alteration was observed in the copper levels of copper IUD wearers with subsequent measurements for a duration of up to 24 months. The mean range and distribution frequency of the serum copper levels in long-term copper IUD users were similar to those observed in the normal population. No difference was found in the 24-hour mean urinary copper excretion between the control group and the copper IUD consumers. It was suggested that released copper from a copper IUD may not be readily absorbed from the uterine fluid [21].

The profiles of iron, calcium, copper, and zinc levels of 17 healthy women, taking either a combination of 0.030 mg of ethinyl estradiol and 0.150 mg of levonorgestrel (n = 9) or a combination of 0.030 mg of ethinyl estradiol and 0.150 mg of desogestrel (n = 8) for oral contraception, were investigated. The blood samplings were performed prior to oral contraception and after 3, 12, and 24 months' contraception, as well as within 2 months after discontinuation of the pill. No alterations were found in iron, calcium, and zinc levels while the copper level was significantly elevated during oral contraception, yet returned to the initial level after discontinuation of contraception. No differences occurred between the two preparations for oral contraception [22]. As it has been already shown in some previous studies women have markedly higher Cu values than men. These differences are evidently due to hormonal and estrogene status, respectively. This fact is supported by evidence that levels of Cu in women using hormonal contraception (with estrogene component) are among the highest. It has been also shown that The hormonal contraception significantly increases the concentration of Cu in blood (920 µg Cu.l-1 vs. 1,270 µg Cu.l-1, $p< 0.01$). It was supposed that estrogens may induce ceruloplasmin synthesis in the liver, which leads to an increase of blood Cu concentration. This deduction was also supported by the observation, that concentration of Cu blood level in young girls (age 10 years, without hormonal activity), when compared with levels in boys of the same age (16, 18) do not differ. The relationship between age and Cu blood level has an increasing tendency in men and decreasing in women. It is possible to explain it by decreasing Levels of sex hormones and their declining activity with increasing age. So, for example in elder men, the relatively lower Cu levels could be related to the testosterone level decline with age. The relationship between Zn and Se levels did also has no alteration tendency in Contraception user. It was found that hormonal contraception did not influence concentrations of Se and Zn in the blood. It has been thought that the decrease in serum zinc could be reflected in a reduction of tissue zinc status due to changes in zinc absorption, excretion or tissue turnover. If these changes occur, the dietary zinc requirement would be greater in women using OCP. Circulating zinc level may be reduced while some tissue level may be increased. Also, the release of zinc from tissues may be depressed in OCP user, OCP therapy may alter the postabsorptive utilizationof zinc [23]. These findings may be important because selenium is currently believed to offer protective benefits against carcinogenesis. Previous investigation showed that progestational agents alone have no effect on serum copper, whereas estrogen alone has a considerable effect on elevating copper and copper binding proteins levels. Apparently increase in copper levels was proportional to the administrated estrogen dose [24]. It has been demonstrated that plasma iron and TIBC increased during contraceptive therapy. However this elevation of iron and TIBC levels did not prevent of the hemoglobin decrease after phlebotomy and no reticulocyte alteration was also observed. These finding may be able to interpret in part the observation that oral COC users who develop iron deficiency anemia show a minor reduction in iron levels. It was concluded that progestogens therapy failed to affects the transferrin levels and substances such as medroxyprogestrone, which are not metabolized to estrogen was observed to be ineffective in changing the transferrin levels. It was suggested that there may be separate mechanisms affecting iron levels and iron binding capacities. Most of the changes observed on iron and TIBC have been attributed to hormone effects on transferring increase. According to these considerations, it was suggested that contraceptive pill may be a protective device for women and may have a beneficial effect in conserving in iron stores. In this connection, mechanisms that were proposed include reduction of menstrual loss, which associated with the pill taking and the possible alteration in TIBC percent saturation may affect increasing iron absorption [25].

COCs and Cardiovascular markers levels alterations

Several studies and reviews have assessed the risk of stroke and MI with the use of different-generation OCs [Table 3]. C-reactive protein; Homocysteine; Nitric Oxide; Lipid Profile levels alterations. Several epidemiological studies have shown a clear association between the use of combined oral contraceptives (COC) and an increased risk of venous and arterial thrombosis [26-35]. It was also identified that COC intake is also associated with increased risk of Atrial Thromosis [32-35]. The studies performed on women receiving hormone replacement therapy (HRT) indicate that the adverse cardiovascular effects may depend on the type, dosage, form, and route of administration of hormones. The relative risk of diseases according to the type, dosage and route of administration will be different. Harms include CHD, stroke, thromboembolic events, breast cancer with 5 or more years of use and cholecystitis [36]. The first formulations of these drugs contained much higher doses of estrogens and progestins than those available today are found to be associated with an unacceptably high rate of unwanted effects including serious cardiovascular events [37]. Many epidemiological studies have evaluated the association between COC consuming and the risk of coronary heart disease and MI. However, the pathogenesis of coronary heart disease is complicated and includes abnormalities in lipids, endothelium and thrombosis. Increasingly inflammation has been recognized as an important component in the coronary artery disease pathway [38]. Due to the impressive alteration in components of COCs and due to a more appropriate prescription of COC excluding women at cardiovascular risk, the results of a review of the epidemiological studies which included women after wide use of third generation pills are available. As it shown in Table 2, the risk of MI associated with the current COC use, regardless of the dose of ethinylestradiol and the type of progestin, from 11 studies including women after 1990. With the exception of two studies, there was an elevation in the risk of MI among users of COC. Using a random effect model meta-analysis, the pooled OR showed a significantly increased MI risk with an OR of 1.7 (95% Confidence interval [CI]: 1.2–2.3). The relationship between COC use and the risk of dying from MI was surveyed. Achieved

Results suggested a slightly increased risk of death among women having an MI associated with exposure to second generation OC, but the absolute risk is very low. Pooled OR of MI among first generation consumers and second generation users were not significantly different (p ¼0.09); Pooled OR of MI among first generation users and third generation users were significantly different (p <0.01); Pooled OR of MI among second generation users and third generation users were not significantly different (p ¼0.23). Recent data shows that use of these pills could be associated with an increased risk of myocardial infarction, especially in women with cardiovascular risk factor such as smoking or hypertension .The studies performed on women receiving HRT indicate that adverse cardiovascular effects may depend on the type, dosage, form and route of administration of hormones [39].

A Population-based cohort study with linkage of 4 national registries between 1995 and 2009 setting 1 626 158 women participants from 15 to 49 years of age showed that of Oral hormonal contraceptives containing ethinyl estradiol were associated with increased risk myocardial infarction (p<0.00i) [40]. Based on the method of administration, many data are available regarding the risk of cardiovascular disease. The relative risk of MI [2.08 (95% CI: 0.67–6.48)] among women who used vaginal ring and no transdermal patch user experienced MI was reported. It is noteworthy to bold that for some specific contraceptives, the number of women who suffering from MI was too small to provide reliable estimates [41]. The MI risk among users of transdermal contraceptive systems and the same component norgestimate containing oral contraceptives was compared by another small study and no difference in MI risk (RR: 1.2; 95% CI:0.3–4.7) among women who used vaginal ring and no transdermal patch user experienced MI was showed. Overall, the relative risk of MI was not significantly elevated for any of the progestin only contraceptives [41].

The cardiovascular safety of oral contraceptives (OCs) containing less than 50 mcg of estrogen and second or third generation progestins was reviewed in a research literature and suggests that these formulations are safer than earlier OCs. Although some recent studies detected an increased risk of venous thromboembolism of 1.5-2.0 in users of OCs containing desogestrel or gestodene

Compared with second-generation progestins. Discrepant results have been achieved by studies of the association between combined OCs and myocardial infarction; one found an increased risk with second but not third generation OCs. Little or no increase in risk in consumers of modern OCs was indicated via some studies without other cardiovascular risk factors. As some available research indicates that up take of second or third-generation OCs carries less risk of venous thromboembolism than pregnancy. In addition to the prevention of pregnancy and its attendant risks, low-dose OCs confer additional health benefits such as reductions in the incidence of ovarian and endometrial cancer [41]. On the other hand, there is a growing awareness of possibility of alterations of some of cardiovascular risk biomarkers in women receiving combined OCPs. Our previous study [42-43] identified that hormonal contraceptive pills consuming can adversely affect different cardiovascular risk biomarkers levels, of which, homocysteine (HCY), CRP and nitricoxide (NO) that are of our particular importance. We demonstrated that consumption of oral contraceptives is associated with elevated serum CRP in women, which may partially explain increased risk of future cardiovascular events [43]. We also showed that homocysteine levels were significantly higher in women receiving OCP in comparison with controls ($P=0.027$ and $p<0.001$, respectively). After 3 months of treatment, No levels were significantly decreased ($P=0.048$). It is known that high levels of homocysteine acerelated to increased risk of venous thrombosis, cardiovascular diseases (CVD), thrombotic, neurodegenerative, pregnancy-associated diseases and disorders of the central nervous system [43]. It was proposed that these alteration in homocysteine and CRP levels in OCP consumers could be attributed to the OCP suggesting that receiving of these pills should be reviewed in women with increased risk of atherosclerosis and other cardiovascular risk factors. The homocysteine and CRP levels increase may have implications for development of cardiovascular diseases and venous or inflammatory diseases. It was proposed that the whole body homocysteine and CRP metabolism could be impaired due to OCPs conversion to reactive species. The results suggested that OCP treatment may induce the formationof free radicals, which could stimulate CRP and homocysteine synthesis. Paobably OCP has a direct effect on Hepatic CRP and homocysteine synthesis. Previous studies have shown that OCPs may directly modulate hepatic synthesis of several factors at the transcriptional level and may also have various immune modulatory effects, therefore predispose to thromboembolic events by stimulating inflammatory mechanism. CRP and homocysteine levels seem to be sensitive to hormonal changes in oral contraceptive users. It was suggested that even a small amount of steroid compounds in OCP could be converted to peroxide and is sufficient to induce synthesis a new molecules of homocysteine and CRP. It has been suggested that decreased bioavailability of nitric oxide (NO may result in abnormal reactions between the vessel wall and platelets and is thus involved in the initiation and progression of atherosclerosis. NO leads to vasodilatation and inhibits platelet aggregation and migration. Reduced bioavailability of NO has been implicated to be involved in the initiation and progression of atherosclerosis. There is evidence for endothelial dysfunction and specific defects in NO mediated vasodilatation in patients with hypertension, smokers, and individuals with elevated concentration of HCY. Several studies have defined that female sex steroids may affect NO and HCY [42-43]. The results of the studies by Ridker et al. [44] conducted on healthy postmenopausal women indicate that cardiovascular risk is increased more than twice in women with moderately increased HCY concentration ,irrespective of the conventional risk factors. HCY level is higher in post-menopausal women in comparison with those in the premenopausal period. This might be due to the effect of OCP on decreasing the availability of group B vitamins for HCY metabolic pathways. HCY metabolic pathways strongly depend on folate, VB12 and B6 vitamins and deficiency of one or more of these vitamins has been implicated as the most common cause of moderately elevated HCY levels among adults. The results of the reports on the effects of OCPs on HCY levels are not consistent. For example, in a study, Merki-Feld et al. [45] showed that long- term (3cycles) treatment with two OCPs of EE/LKG (30 µg ethyinylestrsdiol/150 µg levonorgestrel) and EE/GSD (30 µgethynylestradiol/75µggestodene) increased HCY levels. But, Hanna et al. [46] reported that consumption of the three forms of HRT in three groups of women in the early postmenopausal stage with normal initial concentration of HCY, had no influence on the

HCY levels. These different observations may be due to effects of various endogenous sex hormones, which have been reported to affect HCY levels. For example, it was shown that HCY level is lower during pregnancy and higher in patients with polycystic ovary syndrome. The effects of sex hormones on NO production have been subject of different studies. For example, it has been shown that 17-α-estradiol elevates endothelial NO production in cultured cell and decreases inducible nitric oxide synthase (NOS) in smooth muscle cells of rat aorta. This is in accordance with present study showing that a decrease in NO level is observed during receiving of a combination of ethinylestradiol with levonorgestrel. Interestingly, some studies showed that NO level could be a function of HCY concentration. For example, it has been demonstrated that at high levels, HCY may decrease endothelial production of NO through oxidative mechanisms. In another study it has been found that in monkeys with hyperhomocysteinemia, the level of A symmetric dimethylarginine (ADMA), which is an endogenous inhibitor of NOS, increases. On the other hand, it was shown that treatment with HCY decreases the glutathione peroxidase (GPX) activity, which leads to a high susceptibility of NO to oxidative in activation [42]. Previous reports of the women's Health Initiative[47] demonstrated that progestin,with or without estrogens, increases CRP levels. They identified that progestin in combination with conjugated equineestrogen increases the interleukin 6 (IL6), an inflammatory-mediated stimulation of CRP, and showed that when the subjects were treated only with the equineestrogen, IL-6change was negatively related to CRP change. It was suggested that presence of a progestin causes the IL-6 mediated stimulation of CRP, whereas other mechanisms are likely responsible for CRP production in women receiving only conjugated equine estrogen. They demonstrated that combined regimen of conjugated equineestrogen plus low dose medroxyprogestrone acetate (MPA), which were administrated continuously may have a distinct role in conferring this increased coronary artery disease risk. Cauci et al [48] also showed that third-generation oral contraceptive use increases low-grade inflammatory status measured by high-sensitivity CRP concentrations. Alteration of inflammatory status in oral contraceptive users could affect the risk of venous thromboembolism, cardiovascular disease, and other oral contraceptive-associated Adverse conditions in young women. In another study we [49] indicated that LD COC uptake results in a significant decrease in serum adiponectin concentration, nosignificant increase in leptin levels and a more atherogenic lipid profiles by significantly increasing LDL and no significantly decreasing HDL concentrations. These findings suggested that COC may reduce or stimulate the adiponectin and leptin concentrations, respectively. This might be due to an effect of these pills on adipocyte maturation via inhibition or stimulation of the synthesis of new adiponectin and leptin molecules or may be are result of the increased frequency of a particular allele of the adiponectin and leptin. It was suggested that these alterations in adiponectin and leptin concentrations and lipid profiles may be related to their probable effects in response to various pathological and physiological properties of COC or its metabolites. It has been suggested that probably free radicals produced during metabolism of COCs change the amounts of adipokines, leptin and atherogenic lipids. The effects of lipid metabolism on 98 women who received 2 different types of progestin-only pills, desogestrel 75 mcg/d vs LNG 30 mcg/d were evaluated. There were minimal changes in the lipid profile except for decreasing trends in levels of HDL, its subfractions, and apolipoprotein-I and -II. No differences were observed between the 2 formulations, including LDL and apolipoprotein-B, despite the higher progestin dose found in desogestrel. Third-generation progestins with "lesser androgenicity" may allow more expression" of the effects of estrogen on lipids. A prospective study of 66 women over 9 months comparing either desogestrel (50/100/150 mcg) and EE (35/30/30 mcg) with LNG (50/100/ 150 mcg) and EE (30/40/30 mcg) showed that the desogestrel formulation increased HDL, whereas LNG decreased HDL. Another study compared monophasic desogestrel/EE with triphasic LNG/EE in 37 healthy young women. While both preparations led to an increase in total cholesterol, the desogestrel formulation led to a reduction in the LDL. A 1995 study of DRSP compared with LNG for 6 months showed that HDL increased in the DRSP group ($P<.05$) but triglyceride levels showed a greater increase in the DRSP group ($P<.05$). It was suggested that use of OCs in the absence of risk factors dose not promote coronary heart disease (CAD), and OCs should not be withheld from dislipidemic women [50].

Overall, low dose oral contraceptives have been associated with no increased risk or only small increases in the risk of myocardial infarction or stroke in recent studies of these effects. Sidney et al [51] estimated the incidence of myocardial infarction to be 5.2 per 100,000 users, with the absolute excess risk being approximately 0.3per 100,000 users. Petitti et al. [52], reporting results from the same population, estimated the overall annual incidence of stroke in women aged 15to44years to be 11.3per 100,000 users, with the rate evenly divided between hemorrhagic and ischemic stroke. It was concluded that Stroke is rare among women of childbearing age. Low-estrogen oral-contraceptive preparations do not appear to increase the risk of stroke. The majority of deaths from myocardial infarction (cardiovascular) occur in older oral contraceptive users who smoke. Heavy smoking, in particular, appears to potentate the risk of myocardial infarction in oral contraceptive users, whereas light smoking appears to have an intermediate effect on the risk of myocardial infarction, closer to that of nonsmokers. Women presenting with one of these risk factors and using hormonal contraceptives represent a group at high risk for arterial disease. Therefore, the benefit/risk profile of pill use has to be cautiously assessed for these women before prescribing combined hormonal contraceptive with regard to unintended pregnancy. Similarly, an individual assessment of the benefit/risk profile of pill use has to be performed for women over 35 years. Although differences in risk factors for arterial disease, such as dyslipidemia or hypertension, have been shown between the different types of progestin generations, the risk of arterial events seems to be similar among women using second or third generation pills. Similarly, new routes of administration do not seem to be safer than oral administration. In contrast, only progestin contraceptives, low dose of oral progestin or delivering small doses of intrauterine levonorgestrel, could be safer with respect to arterial risk [53-55]. Recent epidemiological studies [56] have reported an approximately two-fold, significant, increased odds ratio for venous thromboembolism in users of third generation oral contraceptives (OCs) compared to users of second generation OCs. The data show a lower reported incidence of venous thromboembolism with the use of second-generation OCs over time compared to the prior studies, while the incidence of

Venous thromboembolism for use of third-generation OCs is approximately equal to that previously reported for second generation products. Generally, evidence has shown that the risk of venous thromboembolism and the impact on hemostatic parameters are reduced with decreasing estrogen dose. In addition, there is no evidence of a clinically significant effect of the OC progestogen doses on hemostatic parameters. The results of a meta-analysis of eight observational studies [57], did not show an association between progestin-only contraception consumption and an increase risk of venous thromboembolism when compared with nonusers of hormonal contraception. On contrast, four additional epidemiologic studies have revealed a two-fold increased risk of non-fatal venous thromboembolism for OCs containing desogestrel or gestodene compared to levonorgestrel; the excess risk is about 15 per 100,000 events per year. It is noteworthy that association of thromboembolism risk in third-generation OCs users should be took a biologic explanation. It was believed that until there is a biologic interpretation of the greater thromboembolism risk in the third-generation OCs users, this association should not be considered as causal and no change in OC advising practices is warranted for either current or new acceptors. However, smokers over 35 years of age should not use any combination OCs [58]. A systematic review of studies published between January 1995 and April 2010 aimed at determining the effect of combined hormonal contraceptives (CHCs), administered orally, transdermally or vaginally, on the risk of venous thromboembolism (VTE). It was suggested the safest CHCs in terms of VTE are those containing levonorgestrel or norgestimate. The risk of VTE, which associated with desogestrel, drospirenone or cyproterone acetate-containing CHCs is greater than those associated with CHCs containing levonorgestrel regardless of how to get. An increased risk of VTE was found for CHCs with gestodene in comparison with CHCs with levonorgestrel. They showed no differences in VTE risk between oral and transdermal CHCs containing norgestimate or norelgestromin, respectively [59]. Two recent studies, a cohort study from Denmark, and a case-control study from the Netherlands, have reported increased risks of venous thromboembolism (VTE) among users of oral contraceptives (OCs) containing desogestrel, gestodene, drospirenone and cyproterone, relative to levonorgestrel consumption. The evidences

Suggested that increased risk of VTE in OC users is a class effect, dependent on estrogen dose and duration of receiving, and independent of the progestogen used. In the Netherlands case-control study 1524 cases of incident VTE below the age of 50 years were compared with 1524 control women. Overall, the risk of VTE among current users of any OC was significantly increased by some five-fold, relative to non-use, and the higher the estrogen dose, the higher was the risk. In addition, the risk of VTE was highest in the first months of use. Relative to the use of levonorgestrel, the RR for drospirenone was 1.7 [95% CI 0.7–3.9; for desogestrel it was 2.0 (95% CI 1.4–2.8); for gestodene it was 1.6 (95% CI 1.0–2.4); and for cyproterone it was 2.0 (95% CI 1.3–3.0)]. Among women who had used OCs for more than 2 years the risk of VTE for desogestrel "remained increased compared with levonorgestrel, and was similar to the overall risk – for gestodene users the odds ratio was 1.5 (95% CI 0.9–2.60) and for desogestrel 1.9 (95% CI 1.3–2.0)". Among women who used the "newest types of [OCs]" for 3 months or less the odds ratios were 1.9 for drospirenone (95% CI 0.2–21.3) and 1.6 (95% CI 0.3–9.9) for cyproterone. In the Danish study VTE risk is highest soon after stating of OC use, and duration of taking was nonsignificant for levonorgestrel users, but not for drospirenone users; for the remaining compounds duration was only slightly underestimated. The significant lake for levonorgestrel resulted in systematic overestimation of the relative risks for the compared OCs. Only the duration of current use, not duration of all episodes of use was relevant to VTE risk [60]. Attributable risk of death from cardiovascular disease resulting from oral contraceptive use is 0.06 and 3.0 per 100,000 nonsmokers 15 to 34 years of age and 35 to 44 years of age, respectively. In smokers this risk increases, respectively, to 1.73 and 19.4 per 100,000 users in these 2 age groups; however, 97% and 85% of this risk is due to the combined effects of smoking and using oral contraceptives. The attributable risk of death from cardiovascular disease in nonsmoking oral contraceptive users is lower than the risk of death from pregnancy in nonusers of oral contraceptives at all ages; however, among smoking oral contraceptive users more than 35 years of age, the excess risk of death from oral contraceptives is higher than the risk of death from pregnancy. There is virtually no excess attributable risk of death from cardiovascular Disease related to oral contraceptive use in young women. However, smokers more than 35 years of age should use a nonestrogen contraceptive [61]. Combined hormonal contraceptives, menopause hormone treatment and surgery/cast in orthopedic patients are important risk factors for venous thromboembolism (VTE) in women. Women with a positive family history and combined hormonal contraceptive or menopause hormone treatment had an OR of 15.3 (95% CI 6.1-38) and 5.9 (95% CI 3.3-11) respectively compared to women without hormones or family history [62]. Bhargava et al. [63] showed that Oral contraceptive causing renal artery thrombosis. They identified that the of renal artery thrombosis leading to acute renal infarction associated with oral contraceptive use. They showed that after stopping the oral contraceptive consumption in a young female with a haematuria and elevated serum creatine, fever, leucocytosis, elevated lactate dehydrogenase and acute left lower quadrant pain followed by nausea, the fever and leucocytosis was stopped in following 3 days. Extensive thrombophilic work-up was negative and no recurrence of thrombosis was found during a 6-month follow-up period [63]. In systematic review and meta-analysis was adjusted with Peragallo Urrutia R et al., to estimate the risk of venous thromboembolism, stroke, or myocardial infarction (MI) associated with the use of oral contraceptive pills (OCPs) and to describe how these risks vary by dose or formulation, showed that current use of combined OCPs is associated with increased odds of venous thromboembolism and ischemic stroke but not hemorrhagic stroke or MI [64]. In a study by Josse AR et al [65], the effect of Hormonal Contraceptives on emerging cardiometabolic and other disease risk factors was investigated and this result was achieved that HC use was associated with different concentrations of plasma proteins along various disease-related pathways, and these differences were present across different ethnicities. Aside from the known effect of HC on traditional biomarkers of cardiometabolic risk, HC use also affects numerous proteins that may be biomarkers of dysregulation in inflammation, coagulation and blood pressure. In order to compare the effect of combined oral contraceptive (COC) and combined vaginal contraceptive (CVC) methods on the inflammation and procoagulation,. female participants were recruited in 3 groups: control participants, COC users, and CVC users. Different blood biomarkers were measured. The users

Of both COC and CVC had higher levels of C-reactive protein (P < .0001) and factor VII (P < .0001) as comparison with controls [66]. The association between hormonal contraceptive (HC) 2,285 use, and behavior-related and biological cardiovascular risk factors was determined among teenage girls aged 13-17 years in Germany. Prevalence of HC use was determined according to sociodemographic variables, behavior-related health risks, and overweight status. They compared HC users and nonusers with respect to biological cardiovascular risk factors, including systolic and diastolic blood pressure, and serum concentrations of lipids, lipoproteins, high sensitivity C-reactive protein (hs-CRP), and homocysteine. They concluded that HC use among 13-17-year-old girls in Germany is significantly correlated with a more unfavorable cardiovascular risk profile, which is partly explained by a clustering of behavioral risk factors among HC users. It was suggested that avoidable behavioral cardiovascular risk factor should be evaluate by physicians when prescribing HC to teenagers and consultation regarding to the risk profile need to be patient [66-67]. The elevated risk of venous thromboembolism and the transient increase in the risk of coronary heart disease (CHD) during treatment with conjugated equine estrogens and medroxy progesterone acetate (CEE/MPA) but not CEE alone suggests a direct effect of MPA on the vessel wall. MPA has been demonstrated to upregulate the thrombin receptor, the thrombin-induced production of tissue factor and procoagulatory activity in the vessel wall owing to its glucocorticoid activity. In contrast, CEE alone reduced non-significantly the risk of CHD in women aged 50–59 years, suggesting that primary prevention is possible if estrogen replacement therapy is initiated early. MPA has been demonstrated to upregulate the thrombin receptor, the thrombin-induced production of tissue factor and procoagulatory activity in the vessel wall owing to its glucocorticoid activity. In contrast, CEE alone reduced non-significantly the risk of CHD in women aged 50–59 years, suggesting that primary prevention is possible if estrogen replacement therapy is initiated early [68].

COCs and Inflammatory markers levels alterations (IL-6 , PGE2)

The results of many studies suggested that PGE2 I a principal mediator of inflammation in diseases such as rheumatoid arthritis and osteoarthritis. Synthesis Of PGE2, as an immune activator is influenced with hormones. For example, a study conducted on dysmenorrheal adolescents who were treated with the oral contraceptive Lyndiol2.5mg (R) for one cycle, the levels of PGF2a, PGE2, PGI2 metabolites, TXA2, 6- Keto- -PGF1a and TXB2 were tested before, during and after treatment. All PG levels during the treatment cycle (TC) and post treatment cycle (PoTC) were found significantly lower, compared to those of the pretreatment cycle (PrTC). The results of a study by Sato et al [69] investigating the effect of progesterone and17-estradiolon the PGE2 production of the rabbit uterine cervical fibroblasts showed that the progesterone and 17-estradiol prevent the initiation of labor through inhibiting PGE2 production after the suppression of COX-2 production during pregnancy. In our previous study [70], we showed a significant increase in PGE2,LDL-C, cholesterol concentrations, systolic and diastolic blood pressure.

The univariante and multivariate analysis of achieved data showed that COC taking and age together affect the blood pressure significantly. It is noteworthy the results indicated that effect of OCP taking is more remarkable than age. It was suggested that the increase of Prostaglandin E2 and atherogenic lipid levels may be related to their probable effects in response to various pathological and physiological properties of COCs. According to this fact that PGE2 is a principle mediator in inflammation pathway, it was hypothesized that the COCs and their metabolites probably could result in many inflammatory pathological statues. We also showed that these alterations were also accompanied by the finding of a strong and statistically significant elevation of serum LDL-C and cholesterol concentrations and a considerable decrease (no significant) in HDL-C levels of women treated with LD COCs. It was proposed that COC consumption probably leads to an alteration in serum hormonal balance, which might cause a disturbance in lipid metabolism and their profiles. In a study, Barreiros et. al [71] showed that after 1 year of continuous contraceptive consumption, there was a significant increase in triglyceride, total cholesterol (TC), and HDL-C levels. It has been found that the contraceptive induced dyslipidemia has a pro-atherogenic nature, whereas the TC/ HDL-C ratio was unchanged. It was suggested that oral contraceptives with estrogen

Plus progestin are likely to influence on apo lipoprotein B metabolism by changing the expression of different enzymes or receptors that play a major role in this metabolism [71]. It has been demonstrated that 17-Beta estradiol and hydroxyl estradiols together elevate cyclooxygenase 2 expression and prostaglandin E2 secretion in human bronchial epithelial cells. The effect of estradiol (E2) and progesterone(P4) on basal and LH-stimulated PGF2a and PGE2 secretion and cyclooxygenase-2(COX-2) expression in porcine endometrial stoma cells, which obtained on days12–13 of the estrous cycle was examined .The results confirmed the stimulatory effect of LH on PG2aF secretion and COX-2 expression in porcine stoma cells before luteolysis. In contrast, the dienogestas an oral active synthetic progesterone was found to inhibit the PGE2 production. The PGE2 synthesis mRNA, protein expression and the nuclear factor-jB activation were identified to be inhibited by dienogest. The results of a17 beta-estradiol treatment study on PGE2 synthesis pathway showed that17 beta estradiol can inhibit PGE2-induced COX-2 (a key enzyme in PGE2 biosynthesis pathway) expression and cellular motility via suppressing activation of Akt and ERK1/2 in human LOVO colon cancer cells. The achieved data suggested that LD COC taking may result information of the various metabolites which could stimulate the synthesis of anew number of COX-2 enzymes to counteract them. In current study, individuals from the control and COC receiving groups were matched regarding age and other confounding variables, therefore difference in PGE2 levels could attributed to difference in their COX-2 availability or an increased frequency of a various kind of allele for COX-2 or other relevant enzymes, which conduct the lipid metabolism in Iranian subjects. It was suggested that Probably, COC has a direct effect on the synthesis of these biomolecules. Experimental evidences suggest that the metabolic activation of medroxy progesterone acetate and its possible conversion to reactive species is in fact responsible for its probably genotoxicity. It has been revealed that medroxy progesterone acetate is genotoxic through metabolic activation by various forms of quinines similar to estrogens, which generate superoxide, hydrogen peroxide, and ultimately, reactive hydroxyl. The PGE2 and lipids levels seem to be sensitive to hormonal changes in oral contraceptive users. It was suggested that even a small amount of steroid compounds in COC could be converted to peroxide and is sufficient to induce synthesis of new molecules of lipids and PGE2. The role of PGE2 and its receptors on development of cardiovascular and inflammatory diseases were also demonstrated [72-73]

Glintborg D et al. [74] designed the study where ninety patients with PCOS were randomized to 12-month treatment with metformin (M) (2 g/day), M + OCP (150 mg desogestrel + 30 microgram ethinylestradiol) or OCP. Adiponectin, IL-6, MCP-1 and clinical evaluations were performed before and after the intervention period in the 65 study completers. Their results show that Adiponectin, IL-6, and monocyte chemo attractant protein (MCP-1) levels were unchanged during the three types of medical intervention. They concluded that Long-term treatment with M alone or in combination with OCP was associated with improved body composition compared to OCP, whereas inflammatory markers were unchanged. OCP was not associated with increased inflammatory markers despite a small but significant weight gain [74]. The influence of OC on the production of thermoregulatory cytokines, i.e. interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), soluble glycoprotein 130 (s-gp130) and leptin, and that OC-induced changes in oral temperature (T(oral)) are associated with changes in plasma concentrations of these cytokines was investigated by Salkeld BD et al [75]. They showed that (a) leptin implication in basal thermoregulation; (b) progestins have a significant influence on circulating IL-6 concentrations, and (c) plasma CRP concentrations depend upon combined influences of progestins and bioavailable IL-6.

COCs and Systemic High Blood Pressure

Hormonal contraceptives use in Women with hypertension might increases the cardiovascular events risk. Several studies have been shown an increased prevalence of acute myocardial infarction (AMI) and stroke among hypertensive women who use combined oral contraceptives (COCs) when compared with normotensive and hypertensive nonusers. According to the US Medical. Eligibility Criteria for Contraceptive Use (US MEC), women with adequately controlled hypertension or moderately elevated blood pressure (140–159/90–99 mmHg) generally should not use combined hormonal contraceptives (CHCs) (US MEC 3). Women with severely elevated blood

Pressure (≥160/100 mmHg) or with vascular disease should not take CHCs (US MEC 4) and generally should not use depot medroxyprogesterone acetate (DMPA) (US MEC 3). Three case-control studies showed that women who did not have blood pressure measurement prior to initiating combined oral contraceptives (COCs) had a higher risk for acute myocardial infarction (AMI) than women who did have blood pressure measurement. The results of two case-control studies showed that women who did not have blood pressure measurement prior to initiating COCs had a higher risk for ischemic stroke than women who did have blood pressure measurement. No difference in the risk for hemorrhagic stroke among women who initiated COCs based on whether or not blood pressure was measured was found via one case-control study.

The WHO study also examined the association between COC use and ischemic stroke. Odd ratios for ischemic stroke were higher among COC users without measurement of blood pressure prior to current COC use compared to nonusers than among COC users with blood pressure measurement, regardless of age (b35 or ≥35), although CIs overlapped. According to WHO study, Odd ratios for hemorrhagic stroke were not different based on whether or not a woman had blood pressure measurement prior to current COC use [76]. Association between systolic and diastolic blood pressure (SBP and DBP) and oral contraceptives (OC) taking in hypertensive women was also investigated. In a prospective cross-sectional study [77], 171 women who were referred to the Hypertension Outpatient Clinic of Hospital de Clínicas de Porto Alegre; 66 current users of OC, 26 users of other contraceptive methods and 79 women who were not using contraception were evaluated. The average of six blood pressure measurements was used to establish the usual blood pressure of the participants. Current OC users were compared with users of other methods and with patients who were not taking contraception. SBP and DBP among the different groups, and prevalence of uncontrolled hypertension (SBP ≥ 140 mmHg and DBP≥ 90 mmHg) were Main outcome measurements. DBP was higher in OC users (100.2 +/- 15.9 mmHg) than in patients using other contraceptive methods (93.4 +/- 14.7 mmHg) and not taking contraceptives (93.3 +/- 14.4 mmHg, p = 0.016). Women who were

Taking OC for more than 8 years showed higher age-adjusted blood pressure levels than women using OC for shorter periods. Patients using OC had poor blood pressure control (p for trend = 0.046) and a higher proportion of them presented moderate-severe hypertension. These results were independent of antihypertensive drug use. In a logistic regression model, they found that current OC use was independently and significantly (P=0.000) associated with prevalence of uncontrolled hypertension. It was concluded that hypertensive women using OC present a significant increase in both DBP and SBD and poor blood pressure control, independent of age, weight and antihypertensive drug treatment. Consistently, we also showed [49, 70] that OCP taking for at least 3 month cause a significant increase in both DBP and SBD as comparison controls (P=0.000). In a prospective study [78], the association of oral contraceptive consumption before pregnancy and the risk of gestational hypertension and preeclampsia was investigated .It was identified that recent use of oral contraceptives was associated with a reduced risk for developing gestational hypertension. In contrast, there was a suggestion that recent use of OCP was associated with an increased risk of developing preeclampsia, but only among women who had used these agents for ≥ 8 years. The effect of COCs containing estradiol (E2) on the 24-h ambulatory BP and heart rate (HR) in 18 normotensive and normal-weight women with mean age 32.50±7.49 years and body mass index 22.87±4.08 every 30 min with an ambulatory BP device in 18 normotensive healthy non-smoking women prior to (Days 3-6 of menstrual cycle) and after 6 months of use (Days 20-24 of cycle 6) of a COC containing either a quadriphasic combination of E2 valerate plus dienogest (n=11) or a monophasic association of micronized E2 plus nomegestrol acetate (n=7). was investigated by Grandi et al. The achived data suggestd that estradiol-based COCs has a neutral effect on independent risk factors for cardiovascular diseases such as BP or HR [79].

COCs and Cancer: Data based on the impact of COC tanking on cancer is contradictory. Quote from Mr. DAN HELLBERG and ULF STENDAHL in their review article the consequences of OC use in cervical neoplasia have still not been established.a slight but apparent increased risk with long-, but not short-term use of OCs has been found in most,

But not all, studies suggesting a hormonal influence [80]. The International Agency for Research on Cancer classify essteroidal estrogens and estrogen–progestin combinations among agents carcinogenic to human and progestin as possibly carcinogenic. Experimental evidences suggest that the metabolic activation of medroxy progesterone acetate and its possible conversion to reactive species is in fact responsible for its genotoxicity Hana and et al [46] revealed that medroxy progesteroneacetate is genotoxi through metabolic activation by various forms of quinines similar to estrogens, which generate superoxide, hydrogen peroxide and, ultimately, reactive hydroxyl which cause oxidative cleavage of the phosphate sugar backbone of DNA. Evidences from experimental as well as clinical studies indicate the role of oxidative stress in the pathogenesis of heart dysfunction. Protection against oxidative damage is provided by enzymatic and nonenzymatic defenses. In Oxford-FPA study on cancer incidence in relation to oral contraceptive (OC) taking, 17032 women were recruited at family planning clinics at aged 25-39 years between 1968 and 1974 who were using OCs, a diaphragm, or an intrauterine device. Follow-up data were available until 2004. The results showed that OC use had no effect on nonreproductive cancers or on breast cancer. A strong positive relationship was found between cervical cancer incidence and duration of OC taking. On contrast, uterine body cancer and ovarian cancer showed strong negative associations with duration of OC use. The cervical cancer risk was found to be increased and that of uterine body cancer and ovarian cancer was declined by OC use. All these effects elevated with duration of consumption and decreased with interval since last taking. It was suggested that beneficial effects of OC consumption on cancer is preferred to adverse effects [81]. The results of a based case-control study that was conducted in Adelaide, South Australia, and which involved 395 case subjects and 386 control subjects who were aged 20 years to 69 years support those of the majority of previous studies in showing no overall relationship between the use of oral contraceptive agents and the risk of breast cancer [82]. The single HT formulation used in the WHI trial for non hysterectomized women an association of oral conjugated equine estrogens (CEE-0.625 mg/day) and a synthetic progestin, medroxyprogesterone acetate (MPA-2.5 mg/day) increases the risks of venous thromboembolism, cardiovascular disease, stroke and breast cancer.

An observational study, showed an increased breast cancer risk in users of estrogens combined with either medroxy progesterone acetate (MPA), norethisterone, or norgestrel. It is unclear and questionable to what extent these results might be extrapolated to other HRT regimens, that differ in their doses, compositions and administration routes, and that were not assessed in the WHI trial and the MWS [83].

The results of a study conducted by Faber [84] showed that use of combined oral contraceptives only and the mixed use of combined and progestin-only pills decreased the risk of ovarian cancer, while no association was found with exclusive use of progestin-only pills. They showed that no major differences in risk were found for users of combined oral contraceptives with high- and low-potency estrogen and progestin. There was no effect of cumulative progestin intake, but decreased risk of ovarian cancer with increasing cumulative intake of estrogen (OR = 0.82; 95 % CI 0.67-0.99, per 100 mg estrogen) and increasing duration of oral contraceptive use (OR = 0.95; 95 % CI 0.92-0.98, per year of use) were found. No effect of cumulative estrogen intake was found. I a study by Park et al. [85] the outcomes of second round of fertility-sparing management using progestin was surveyed in patients with recurrent endometrial cancer after successful fertility-sparing management. Progestin re-treatment in patients with recurrent endometrial cancer was effective and safe. Therefore, this can be recommended for young women who still want to preserve fertility at recurrence after complete response to progestin. It has been identified that risk of colorectal cancer is reduced among users of oral contraceptives or menopausal hormone therapy. To help understand possible mechanisms through which exogenous and endogenous hormonal exposures are involved in colorectal cancer, they evaluated the risk of these malignancies according to tumor expression of estrogen receptor-β (ESR2). In a population-based study of postmenopausal women (503 cases and 721 controls matched for sex and age), the incidence of the colorectal cancer was determined in 445 cases via immunohistochemical assay of the ESR2 expression. Unconditional logistic regression in case-case analyses were used to evaluate the heterogeneity between risk associations according to ESR2 status. They showed that, colorectal cancer risk significantly decreased with duration

Of oral contraceptive consumption and duration of menopausal hormone therapy for ESR2-positive tumors but not ESR2-negative tumors. A significant heterogeneity was found for the association with the current taking of menopausal hormone therapy according to ESR2 expression but not reproductive factors. They suggested that hormone taking decreases the risk for ESR2-positive colorectal cancer but not ESR2-negative [86]. Because many breast tumors may have their growth stimulated by estrogen, it is reasonable to think that estrogen-containing contraceptives might increase the risk of breast cancer. Several large case-control studies have shown there is no increase in the risk of breast cancer among current and former users of combined contraceptives; however these studies focused on older women. There is some evidence of an increased risk of breast cancer among young oral contraceptive users compared to young non-users. It is important to keep in mind that the number of young women who get breast cancer is very, very low and most breast cancers are diagnosed in post-menopausal women

COCs and Stroke: Stroke is an important public health problem throughout the world because it is a leading cause of death and disability. Epidemiological studies have shown an increased risk of venous thrombosis in women taking third-generation oral contraceptives, ie, those containing the progestogens desogestrel or gestodene. This study assessed the risk of ischemic stroke with several types of oral contraceptives. Two hundred three women with an ischemic stroke and 925 control women were included. The risk of stroke in women using any type of oral contraceptives versus none was 2.3 (95% CI 1.6 to 3.3). Current users of first-generation oral contraceptives had an odds ratio of 1.7 (95% CI 0.7 to 4.4). Low-dose second-generation oral contraceptives was found to increase the risk of stroke 2.4 times (95% CI 1.6 to 3.7), and third-generation oral contraceptives elevated the risk of stroke 2.0 times (95% CI 1.2 to 3.5). They showed that risk of stroke in women using third-generation oral contraceptives was not different from that in women using second-generation oral contraceptives (odds ratio 1.0, 95% CI 0.6 to 1.8). It was concluded third-generation oral contraceptives (containing desogestrel or gestodene) confer the same risk of first ischemic stroke as second-generation oral contraceptives (containing levonorgestrel) [87].

The first case reports regarding deep vein thrombosis (DVT) in women consuming OCs were published shortly after their first prescription. The main cause of these problems was the strong dose of estrogens. The development of OCs with lower estrogen doses dramatically reduced the risk. However, when third-generation pills were developed, different initial studies suggested that those preparations increased DVT risk. In 1995, publications of the WHO cardiovascular disease group of experts, followed by various other studies, suggested that third-generation pills induced a two to four fold relative risk of DVT compared with levonorgestrel-containing OCs. On the other hand, three other studies were unable to find any increase in the risk for DVT in third-generation pill users. The DVT risk returned to baseline after stopping of OCs taking. OCs elevates prothrombin, Factors VII, VIII and X, fibrinogen and prothrombin fragment levels and decline Factor V levels. Those alterations seem to be more important with third than second generation OCs and are associated with an increased risk of DVT. In addition, OCs induce a resistance to activated protein C, also observed in Factor V Leiden mutation carriers, resulting in a decreased sensitivity to the anticoagulant action of activated protein C. It was demonstrated that third generation OCs caused a more impressive resistance. The molecular basis of this achieved resistance is unknown, but it can be in part explained by the decreased level of cofactors of the activated protein C. Additionally, different fibrinolytic variables are changed by OCs (plasminogen, tissue plasminogen activator, plasminogen activator inhibitor type I and plasmin-antiplasmin complexes), which theoretically result in increased fibrinoloytic activity. The clinical implications of these changes are unknown. Finally, prothombotic effects of third-generation pills could be explained on the one hand by the increase in procoagulant effect, and on the other hand by the decrease in anticoagulant effects. These effects appear to be more important with third-generation pills than with second-generation ones. This is probably an example of the complexity of the pharmacological effects of steroids. Although estrogen doses are lower, third-generation progestagens may potentiate the estrogenic effects on clotting factors, thus resulting in a procoagulant effect [88]. In the a case-control study designed by Heinemann[89] , conclude that high doses of EE (≥ 50 mcg) were associated with increased risk of

Stroke compared to formulations with 50 mcg of EE (OR:5.3; 95% CI: 2.6-11 versus OR: 1.53; 95% CI: 0.71-3.31). Other epidemiological studies have also shown an increased risk of venous thrombosis in women taking third-generation oral contraceptives, ie, those containing the progestogens desogestrel or gestodene.

A study evaluates the risk of ischemic stroke with several types of oral contraceptives. Two hundred three women with an ischemic stroke and 925 control women were included. The risk of stroke in women using any type of oral contraceptives versus none was 2.3 (95% CI 1.6 to 3.3). Current users of first-generation oral contraceptives had an odds ratio of 1.7 (95% CI 0.7 to 4.4). Low-dose second-generation oral contraceptives increased the risk of stroke 2.4 times (95% CI 1.6 to 3.7), and third-generation oral contraceptives increased the risk of stroke 2.0 times (95% CI 1.2 to 3.5). The risk of stroke in women using third-generation oral contraceptives was not different from that in women using second-generation oral contraceptives (odds ratio 1.0, 95% CI 0.6 to 1.8). It was concluded that third-generation oral contraceptives (containing desogestrel or gestodene) confer the same risk of first ischemic stroke as second-generation oral contraceptives (containing levonorgestrel. Whereas previous studies have strongly suggested that third generation oral contraceptives are associated with a higher risk of venous thrombosis than second-generation oral contraceptives, particularly in young healthy women. Therefore, in these women, second-generation oral contraceptives are a better choice [90-91].

A review by Francisca [92] provides an update of knowledge regarding venous thromboembolism (VTE) and combined hormonal contraceptives (CHCs) in the light of new progestins and new administration routes for CHCs. The association between the use of combined oral contraceptives (COCs) and an increased risk of VTE has been known about for many years, it being related mainly to the dose of oestrogen; however, recent research has also shown the influence of the type of progestin. When compared to COCs containing levonorgestrel or norethisterone, those containing desogestrel or gestodene present a two-fold greater risk of VTE; for COCs containing cyproterone acetate, the risk is four-fold greater, while there are no or insufficient data for those containing norgestimate, chlormadinone acetate Or drospirenone. With regard to the contraceptive patch, the available data suggest that the risk of VTE is similar to that observed with COCs. The greatest risk of COC-associated VTE occurs during the first year of use, thus suggesting the existence of a predisposing condition, such as being a carrier of a thrombogenic mutation with which the COCs would exert a synergistic effect. Routine screening for such conditions is not justified. Changes in haemostatic variables produced by COCs, for example, acquired resistance to protein C, could be linked to VTE, although it has yet to be demonstrated that such alterations are related to a clinical risk of VTE among COC users [92].

However, four additional epidemiologic studies have revealed a two-fold increased risk of non-fatal venous thromboembolism for OCs containing desogestrel or gestodene compared to levonorgestrel; the excess risk is about 15 per 100,000 events per year. Until there is a biologic explanation of the greater thromboembolism risk in users of third-generation OCs, this association should not be viewed as causal and no change in OC prescribing practices is warranted for either current or new acceptors. However, smokers over 35 years of age should not use any combination OCs [93].

In a study, which conducted by Susan et al [94] the risk of non-fatal venous thromboembolism in women receiving oral contraceptives containing drospirenone with that in women receiving oral contraceptives containing levonorgestrel was compared? It was found that risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone was found to be around twice that of users of oral contraceptives containing levonorgestrel.

In a study on 85 women who were diagnosed with VTE ceriteria, two of whom were users of progestagen-only OCs. Of the 83 cases of VTE associated with use of combined OCs, 43 were recorded as deep-vein thrombosis, 35 as pulmonary thrombosis, and five as venous thrombosis not otherwise specified. The crude rate of VTE per 10,000 women was 4.10 in current users of any OC, 3.10 in users of second-generation OCs, and 4.96 in users of third-generation preparations. After adjustment for age, the rate ratio of VTE in users of third-generation relative to second-generation OCs was 1.68 (95% CI 1.04-2.75). Logistic regression showed no significant difference

In the risk of VTE between third-generation and second-generation OCs users. Among third-generation progestagens users, the risk of VTE was higher in users of desogestrel with 20 g ethinyloestradiol than in users of gestodene or desogestrel with 30 g ethinyloestradiol. With all second-generation OCs as the reference, the odds ratios for VTE were 3.49 (1.21-10.12) for desogestrel plus 20 g ethinyloestradiol and 1.18 (0.66-2.17) for the other third-generation progestagens [95].

Previous studies have reported that users of the 'third-generation' oral contraceptives (OCs) containing the progestins gestodene and desogestrel have about twice the risk for venous thromboembolism (VTE) compared to users of older OCs containing levonorgestrel. Assessments of the risk for VTE among users of norgestimate-containing OCs compared to other Ocs was undertook. It was concluded that risk of nonfatal VTE among users of desogestrel-containing OCs was significantly elevated compared to that of levonorgestrel-containing OCs. The risk of VTE in users of norgestimate-containing OCs was found to be closely similar to that of users of levonorgestrel-containing OCs. The incidence rate ratios for norgestimate-containing OCs compared to levonorgestrel-containing OCs and desogestrel-containing OCs compared to levonorgestrel-containing OCs were identified 1.1 (95% CI, 0.8–1.5) and 2.0 (95% CI, 1.4–2.7), respectively [96].

In a meta-analysis, 3110 publications were retrieved through a search strategy; 25 publications reporting on 26 studies were included. Incidence of venous thrombosis in non-users from two included cohorts was 1.9 and 3.7 per 10 000 woman years, in line with previously reported incidences of 1-6 per 10 000 woman years. Combined oral contraceptives consumption increased the risk of venous thrombosis compared with non-use (relative risk 3.5, 95% confidence interval 2.9 to 4.3). The relative risk of venous thrombosis for combined oral contraceptives with 30-35 μg ethinylestradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone were similar and about 50-80% higher than for combined oral contraceptives with levonorgestrel. A dose related effect of ethinylestradiol was observed for gestodene, desogestrel, and levonorgestrel, with higher doses being associated with higher thrombosis risk. It was concluded that all combined

Oral contraceptives, which investigated in this analysis were associated with an increased risk of venous thrombosis.It was suggested that effect size depended both on the progestogen used and the dose of ethinylestradiol. They observed that all generations of progestogens were associated with an increased risk of venous thrombosis and that third generation users had a slight increased risk compared with second generation users. All individual types of combined oral contraceptives increased thrombosis risk compared with non-use more than two-fold. The highest risk of venous thrombosis was found among 50LNG users, and the risk was similar in 30DRSP, 35CPA, and 30DSG users. Users of 30LNG, 20LNG, and 20GSD had the lowest thrombosis risk [7]. Despite the low incidence of venous thrombosis about three per 10000 woman years among women of reproductive age, the effect of combined oral contraceptives on venous thrombosis is large. Because the oestrogen compound (ethinylestradiol) in combined oral contraceptives probably cause the increased risk in thrombosis. There was an association between declined dose of ethinylestradiol and decrease in the risk of venous thrombosis. Apart from adjustments in the dose of ethinylestradiol, the progestogen compound was also altered in an effort to reduce side effects. However, the combined oral contraceptives users with third generation progestogens show a higher risk of venous thrombosis than those using second generation progestogens. Other progestogens have been developed after the introduction of third generation progestogens that is, drospirenone (introduced in 2001). The thrombosis risk for contraceptives with drospirenone was found to be higher than for combined oral contraceptives with second generation progestogens. The thrombosis risk for contraceptives with drospirenone was found to be higher than for combined oral contraceptives with second generation progestogens [7].

Overall, despite the low incidence of venous thrombosis, the risk in women using combined oral contraceptives could be a real concern because of the widespread use of these contraceptives. Risk of venous thrombosis for combined oral contraceptives with 30-35 μg ethinylestradiol and gestodene, desogestrel, cyproterone acetate and drospirenone were identified to be similar, and about 50-80% higher than with levonorgestrel. The combined of 30 μg ethinylestradiol with levonorgestrel as

A safe oral contraceptive with the lowest possible dose of ethinylestradiol and good compliance was suggested to prescribed [7].

COCs and migraine: Migraine is very common in women during child-bearing years. The type of migraine is important when considering the risk of stroke. Women with migraine without aura have a low risk of stroke and venous thromboembolism (VTE), similar to women without migraine. Combination OC are not recommended for some women with migraine. The women with migraine with aura are recommended to avoid combination contraceptive use via World Health Organization (WHO). The American College of Obstetricians and Gynecologists (ACOG) recommends using alternative forms of contraception in certain populations of women such as women over 35 years who smoke and women with migraine headaches. The most commonly used forms of oral contraceptives (OC) are a combination of ethinylestradiol and a progestin and the progestin-only containing OC, often referred to as the "mini-pill" is less commonly used .In the medical literature the theory that oral contraceptives taking prevent migraine is not fully supported. A low-dose (35 mcg ethinylestradiol or less) monophasic OC may be used in most women with migraine. On the other hand no sufficient data suggest that lower dose formulations of 20-30 mcg ethinylestradiol are safer than the 35 mcg when investigating at VTE or ischemic stroke risk. Using the OC in a continuous-dose regimen may theoretically help prevent menstrual migraine. An incidence of headache of 9.7% in women using extended-regimen OC vs. 17.3% in those using standard regimen OC was reported. Any monophasic oral contraceptive can be adapted to be used in a continuous (extended) fashion. The OC should be discontinued if migraines worsen after the first few months of treatment or if the patient develops aura. Close collaboration among all treating health care providers is essential in caring for this large population of women migraine patients who need or want oral contraception [98]. Several case-control studies and meta-analysis have reported a synergism between migraine and use of COCs on the risk of ischemic stroke. It is now commonly accepted that, in migraine with aura, the use of combined oral contraceptives is always not recommended, and that their intake must also be stopped by patients who suffering from migraine without Aura if aura symptoms appear. The newest combined oral contraceptive formulations are generally well tolerated in migraine without aura, and the majority of migraine without aura sufferers do not show any problems with their use; nevertheless, at least two evidences related to the combined oral contraceptives consumption: exogenous hormone-induced headache and estrogen-withdrawal headache are identified by the last International Classification of Headache Disorders. As regards the safety, even if both migraine and combined oral contraceptive intake are associated with an increased risk of ischemic stroke, migraine without aura per se is not a contraindication for combined oral contraceptive use. When prescribing combined oral contraceptives in migraine without aura patients, in particular in women aged over 35 years, other risk factors (tobacco use, hypertension, hyperlipidemia, obesity and diabetes) must be carefully considered. Furthermore, the exclusion of a hereditary thrombophilia and of alterations of coagulative parameters should precede any decision of combined oral contraceptive prescription in migraine patients [99].

Combination OC use increases a woman's risk for VTE and ischemic stroke. Observational studies found 1-3 additional cases of VTE among 10,000 women taking combination contraceptives for one year. Taking into account a baseline 10-year ischemic stroke rate of 2.7 per 10,000 young women (ages 25-29) years, OC usage increases the risk to 4.0. The risk increases to 11.0 for women who have migraine with aura, and to 23.0 for women with migraine with aura using OC [99]. In 2003, WHO convened an Expert Working Group to review medical eligibility criteria for contraceptive use. After reviewing the evidence provided above the group determined that women with nonmigrainous headaches can use COCs (WHO Category 1), women having migraine without aura who are less than age 35 can generally use COCs (WHO Category 2), women having migraine without aura who are 35 years or older generally should not use COCs (WHO Category 3) and women having migraine with aura, at any age, should not use COCs (WHO Category 4). In addition, WHO made recommendations regarding continued use of COCs among women with headaches and noted that any new headaches or marked changes in headaches while using COCs should be evaluated.

If nonmigrainous headaches develop while taking COCs, the woman can generally continue COC use (WHO Category 2); if a woman develops migraine without aura while she is taking COCs and she is less than 35 years, she should generally not continue to use COCs (WHO Category 3); and if she develops migraine without aura at age 35 years or older or if she develops migraine with aura at any age while taking COCs, she should not continue to use COCs (WHO Category 4) [99].

BMI and obesity and contraceptives: Obesity is defined based on body mass index (BMI), which is an indirect measure of body fat. BMI has been shown to correlate well to direct assessments of body fat. BMI is calculated by dividing weight in kilograms by height in meters squared. Although BMI is not a perfect indicator of body fat, it is reliable, inexpensive and easy to perform in a clinical setting. BMI categories are defined by the Centers for Disease Control and Prevention and The World Health Organization as:

- Underweight b18.5 kg/m2
- Normal 18.5–24.9 kg/m2
- Overweight 25–29.9 kg/m2
- Obese 30–39.9 kg/m2 or Class I obesity 30–34.9 kg/m2 and Class II obesity 35–39.9 kg/m2
- Very obese ≥40 kg/m2 or otherwise referred to as severe, extreme, morbid or Class III obesity.

An effective contraceptive method taking in women with chronic medical conditions, like obesity, is preeminent because these women are at higher risk of pregnancy-related complications. Effectiveness of oral contraception (combined and/or progestin only) may be impaired in overweight and obese women. It has been shown that healthy obese women taking combined hormonal contraception (pill, patch, ring) moderately evaluate their risk of VTE as compared to no obese combined hormonal contraceptive users, but this is not a contraindication to use as it is still less than the risk of VTE associated with pregnancy. Overall, hormonal contraception appears to have little effect on baseline body weight when studied in a nonobese female population. Effectiveness of oral contraception may be impaired in women undergoing bariatric surgery that causes gastrointestinal malabsorption (jejunoileal bypass, biliopancreatic diversion with/without duodenal switch, and Roux-en-Y bypass) and thus should be avoided [100].Weight gain is a commonly perceived Side effect of hormonal contraception and may cause women to avoid or discontinue contraceptive methods. Prior studies have shown weight gain and changes in body composition among users of depot medroxyprogesterone acetate (DMPA). DMPA as an aqueous suspension of 17-acetoxy 6-methyl progestin is administered by intramuscular injection for long-term contraception [101]. Weight change was variable among women using progestin-only contraceptives. Black race was a significant predictor of weight gain among contraceptive users. A previous36-months longitudinal study of 703 women taking contraceptive found that DMPA users had a 5.1-kg weight gain compared to 1.5-kg gain among oral contraceptive users (pb.001) and 2.1kg gain among non-hormonal contraceptives users (pb.001). In addition, DMPA users had a greater increase in total body fat and percent body fat. The perception of weight gain is clinically important, because it may affect a woman's satisfaction with her contraceptive method or influence a woman's decision to continue use of the method. Due to several adverse physical and mental health effects that commonly is associated with obesity, it is important for clinicians to be aware of their patients' weight gains. Understanding that some contraceptive methods have higher rates of perceived weight gain could prove helpful to clinicians when counseling their patients [102].

It was shown that risk of venous thromboembolism is increased with obesity, and this risk may be additive when using a combined hormonal method. According to The World Health Organization (WHO) report ~56.7% of reproductive-age women in the United States are overweight (body mass index [BMI] between 25 and 29.9 kg/m2) and >30% are obese (BMI >30 kg/m2). There are increasing proportions of overweight and obese females in other developed nations as well. In the United Kingdom, >24% of reproductive age women are obese; in Australia 20% of women are also obese. On the other hand, obesity may also impact the efficacy of combined hormonal contraception (CHC), particularly the oral contraceptive (OC) [103].

One possible mechanism of this effect is dilution; steroids may have declined the availability due to increased circulating blood volume or fat sequestration. Obese women may also have different metabolism of steroids than normal weight women. A recent study looking at the impact of obesity on the pharmacokinetics

Of OCs suggests that the ability to reach steady state of hormone levels is decreased in obese women. It may take 3 to 5 days longer for hormone levels in obese women to achieve the steady state levels necessary to allow for hypothalamic pituitary ovarian inhibition.

It was suggested that women with a body mass index (BMI) greater than 30 should be counselled regarding an increased risk of venous thromboembolism (VTE), and consider contraceptive methods other than the combined oral contraceptive pill (COCP) [103].

Although in paradoxically, in a review of the existing literature, Trussell et al. found no convincing evidence that very heavy or obese women have a higher risk of OCP failure during perfect use than thinner women, even with the lowest dose formulations [104].

COCs and Diabetes: The prevalence of diabetes mellitus is increasing dramatically worldwide, resulting in more and more women of reproductive age being affected by either type 1 or type 2diabetes. Management of contraception is a major issue due to the specific risks associated with pregnancy and those potentially induced by hormonal contraceptives in diabetic women. Prescription of combined hormonal contraception in type 2 diabetic women must also be considered with caution due to a frequent association with obesity and vascular risk factors which increase both thromboembolic and arterial risks.

Due to their metabolic and vascular safety profile and according to patient wishes , progestin-only contraceptives, as well as non-hormonal methods, represent alternatives [105]. In a study conducted by Bender et al. the metabolic effects of progestin-only long-acting reversible contraception [levonorgestrel-releasing intrauterine system (LNG-IUS) and etonogestrel implant (ENG-I)] were investigated in normal-weight women but not in obese [body mass index >30kg/m]. They showed that fasting glucose (FG) of ENG-I users was elevated, while their insulin sensitivity decreased to a more extent than LNG-IUS users in comparison with subjects using nonhormonal method.

The observed FG and insulin sensitivity alteration in the obese progestin-only contraceptive users could suggest that either progestin-only LARC method may be safely used clinically [106].

The effect of a long–acting injectable progestin, depomedroxyprogesterone acetate (DMPA) on diabetes risk in Latino women with prior gestational diabetes mellitus (GDM) was studied. Diabetes prevalence rate of the DMPA group was found (19%) more than COC group (12%). The weight gain of the DMPA group during consumption was identified higher (Average 1.8 Kg) significantly (P=0.0001) than COC group. They concluded that DMPA consumption is associated with an increased diabetes risk that could be explained by three factors: 1) use in women with increased baseline diabetes risk, 2) weight gain during taking, and 3) use with high baseline triglycerides and/or during breast-feeding [107].

Serum adiponectin, resistin and markers of adipocyte development (DLK-1) levels in reproductive-age female rhesus macaques monkeys of normal (n=5, mean=5.76kg) and inherently obese (n=5, mean=8.11kg) weight were determined before, during and 2 months after stop taking COC of 8 months of continuous treatment with COCs. The obese group alone showed a significant decrease ($p<.01$) in weight with COC use, which returned to baseline after COC cessation. In the obese group, the baseline adiponectin levels prior to COC treatment were lower ($p<.05$). Adiponectin levels elevated from baseline in both groups, but was higher in the obese group ($p<.05$). Resistin levels was similar at baseline, with an increase in both groups following treatment. Circulating resistin remained increased above baseline levels after stop taking COC, particularly in the obese group ($p<.05$). While DLK-1 levels did not change significantly in either group, a tendency for higher levels was observed in obese animals. It was suggested that COC taking may change metabolic processes via direct (resistin) or indirect (adiponectin) means, while unchanging DLK1 levels suggest that COC do not affect adipocyte development. It was suggested that COCs may directly increase the resistin levels, as observed in both groups. It was also concluded that as adiponectin levels is inversely related to adipocyte mass, therefore increased levels in the obese group are likely attributed to weight loss [108]. A cross-sectional associations between 1) current use of oral contraceptives (OCs) and 2) glucose levels, insulin levels, and diabetes in young adult, who were in the Coronary Artery Risk Development in Young Adults (CARDIA) was investigated

In a prospective observational study of African-Americans and whites aged 18–30 years at enrollment in 1985–1986 by Kim et al. [109] They also studied the effect of current use of OCs on incident diabetes at year 10 of the study.

In consistent with many current reports, they showed that in unadjusted analyses, current use was associated with lower regression coefficients and odds ratios (95% CIs) for dependent variables (fasting glucose, fasting insulin, diabetes, and hyperinsulinemia fasting glucose levels [−3.1 mg/dl, 95% CI (-3.7, -2.5)] and decrease in the odds of diabetes [odds ratio 0.56 (0.32, 0.97)], but not lower fasting insulin levels [-0.01 μU/ml (-0.03, 0.02)], compared with nonuse in both African-American and white women. After adjustment for covariates, current use of OCs was still associated with lower fasting glucose levels [−1.8 mg/dl (-2.4, −1.3)] and lower odds of diabetes [odds ratio 0.56 (0.33, 0.95)], although the associations were attenuated. After adjustment, the association between current use of OCs and higher insulin levels [0.12 μU/ml (0.006, 0.23)] was concluded. No association was found between pattern of use of OCs and incident diabetes at year 10, although the total number of new persons with diabetes at year 10 was small (n = 17).

It was concluded that observed association between Current OCs taking and lower glucose levels in young African-American and white women might be associated with lower odds of diabetes [109].

Conclusion

It is recommended to carry out further study including larger population to elucidate these biochemical biomarkers levels alteration to correlate with side effects caused by hormonal contraceptive so that attempt could be made to mitigate those.

Although the oral contraceptive pills consumption is the safe and effective means to prevent pregnancy but according to the alteration of many biochemical parameters during COCs consumption as mentioned above, a more comprehensive study is needed to justify the side effects of these pills scientifically.

SO, here the conclusion of a number of the studies is reviewed. In order to achieve the more convincing results in this subject, we urgently require future research on large population.

Table 1: Oral contraceptives; A review of the options

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
Progestin only	Norethindrone acetate	Aygestin	-	5	Monophasic	Monthly
	Norethindrone only	Camila, Errin, Jolivette, Nora-BE, Nor-QD, Ortho Micronor	-	0.35	Monophasic	Monthly
First-generation progestin	Ethinyl estradiol and ethynodiol diacetate	Demulen*	Days 1-21: 0.05 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
		Kelnor, Zovia	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	
	Ethinyl estradiol and norethindrone	Gildess Fe 1/20† Junel 1/20, Junel 1/20 Fe,† Loestrin 21 1/20, Loestrin 1/20 Fe,† Microgestin 1/20, Microgestin 1/20 Fe†	Days 1-21: 0.02 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly
		Gildess 1.5/30 Fe,† Junel 1.5/30, Junel 1.5/30 Fe,† Loestrin 21 1.5/30, Loestrin 1.5/30 Fe,† Microgestin 1.5/30, Microgestin 1.5/30 Fe†	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 1.5 Days 22-28: inert pills	Monophasic	Monthly
		Balziva, Femcon Fe,† Ovcon 35, Zenchent, Zeosa†	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-21: 0.4 Days 22-28: inert pills	Monophasic	Monthly
		Brevicon, Modicon, Nelova, Necon 0.5/35,* Nortrel 0.5/35	Days 1-21: 0.035 Day 22-28: inert pills	Days 1-21: 0.5 Day 22-28: inert pills	Monophasic	Monthly
		Cyclafem 1/35, Genora 1/35, Necon 1/35, Norethin 1/35, Norinyl, Nortrel 1/35, Ortho-Novum 1/35	Days 1-21: 0.035 Day 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Monophasic	Monthly

Oral cotraceptives: A review of the options (continued)

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
First-generation Progestin (continued)	Ethinyl estradiol And Norethindrone (continued)	Ovcon 50	Days 1-21: 0.05 Days22-28 Inter pills	Days1-21: 1 Days22-28: Inter pills	Monophasic	Monthly
		Loestrin 24 Fe	Days 1-24: 0.02 Days 25-28: Inter pills	Days 1-24: 1 Days25-28: Inter pills	Monophasic	Monthly
		Necon 10/11*	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-10: 0.05 Days 11-21: 1	Biphasic	Monthly
		Aranelle, Leena, Tri-Norinyl	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-7: 0.05 Days 8-16: 1 Days17-21: 0.5 Days22-28 inert pills	Triphasic	Monthly
		Estrostep Fe† Tri-Legest Fe† Tilia Fe†	Days 1-5: 0.02 Days 6-12: 0.03 Days 13-21: 0.035 Days 22-28: inert pills	Days 1-21: 1 Days 22-28: inert pills	Triphasic	Monthly
		Cyclafem 7/7/7 Necon 7/7/7, Notrel7/7/7, Ortho-Novum7/7/7	Days 1-21: 0.035 Days 22-28: inert pills	Days 1-7: 0.5 Days 8-14: 0.75 Days15-21 1	Triphasic	Monthly
Second generation Progestin	Ethinyl estradiol And Levonorgestrel	Alesse, Aviane Lessina, Levlite, Lutera, Sronyx	Days 1-21: 0.02 Day 22-28: inert pills	Days 1-21: 0.1 Days 22-28: inert pills	Monophasic	Monthly

Oral cotraceptives: A review of the options (continued)

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs multiphasic	Monthly vs extended cycle
Second-generation Progestin (continued)	Ethinyl estradiol And Levonorgestrel (continued)	Altavera, Levlen*, Levora,* Microgynon, Nordette,* Overanette, Portia*	Days 1-21: 0.03 Days22-28 Inter pills	Days1-21: 0.15 Days22-28: Inter pills	Monophasic	Monthly
		Enpresse, Levonest,* Triphasil,* Tri-Levlen,*Trivora	Days 1-6: 0.03 Days 7-11: 0.04 Days12-21: 0.03 Days22-28: Inter pills	Days 1-6: 0.05 Days 7-11: 0.075 Days12-21: 0.125 Days22-28: Inter pills	Triphasic	Monthly
		Lybrel	Days 1-28: 0.02	Days 1-28: 0.09	Monophasic	365-day cycle
		Loseasonique	Days 1-84: 0.02 Days 85-91: 0.01	Days 1-84: 0.01	Monophasic	91-day cycle
		Introvale, Jolessa, Quasense, Seasonale	Days 1-84: 0.03 Days 85-91: inert pills	Days 1-84: 0.15 Days 85-91: inert pills	Monophasic	91-day cycle
		Seasonique	Days 1-84: 0.03 Days 85-91: 0.01	Days 1-84: 0.15	Monophasic	Monthly
	Ethinyl estradiol And norgestoral	Cryselle-28, Lo/Ovral-28, Low-Ogestrel*	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 0.03 Days 22-28: inert pills	Monophasic	Monthly
		Ovral-28, Ogestrel	Days 1-21: 0.05 Days 22-28: inert pills	Days 1-21: 0.05 Days 22-28: inert pills	Monophasic	Monthly
Thrid-generation Progestin	Ethinyl estradiol And norgestoral	Desogen, Emoquette, Ortho-Cept, Reclipsen,Solia	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 0.15 Days 22-28: inert pills	Monophasic	Monthly
		Azurette, Kariva, Mircette	Days 1-21: 0.02 Day 22-23: inert pills Days 24-28: 0.01	Days 1-21: 0.15	Biphasic	Monthly

Oral Contraceptives: A review of the option(continued)

	Generic name	Brand name	Estrogen dose (mg)	Progestin dose (mg)	Mono- vs Multiphasic	Monthly vs extended cycle
Thired-generation Progestin (continued)	Ethinyl estradiol And desogestrel (continued)	Caziant, cesia, Cyclessa, Velivet	Days 1-21: 0.025 Days22-28 Inter pills	Days1-7: 0.1 Days8-14: 0.125 Days15-21: 0.15 Days22-28: Inter pills	Triphasic	Monthly
	Ethinyl estradiol And norgestergal	Mononessa, Ortho-Cyclen, Previfem, Sprintec	Days 1-21: 0.035 Days 22-28: Inter pills	Days 1-21: 0.25 Days22-28: Inter pills	Monophasic	Monthly
		Ortho Tri-Cyclen Lo, Tri- Lo-Sprintec, TriNessal Lo	Days 1-21: 0.035 Days 22-28: Inter pills	Days1-7: 0.18 Days8-14: 0.215 Days15-21: 0.25 Days22-28: Inter pills	Triphasic	Monthly
		Ortho Tri-Cyclen , TriNessa, Tri-Previfem, Tri-Sprintec	Days 1-21: 0.035 Days 22-28: Inter pills	Days1-7: 0.18 Days8-14: 0.215 Days15-21: 0.25 Days22-28: Inter pills	Triphasic	Monthly
Miscellaneous Progestin	Ethinyle estradiol And drospirenone	Beyaz,‡Giainvi,Yaz	Days 1-21: 0.02 Days 25-28: inert pills	Days 1-21: 3 Days 25-28: inert pills	Monophasic	Monthly
		Ocella, safyral,‡ Yasmin, zarah	Days 1-21: 0.03 Days 22-28: inert pills	Days 1-21: 3 Days 22-28: inert pills	Monophasic	Monthly
	Estradiol Valerate And dienogest	Natazia	Days 1-2:3 Days 3-7:2 Days8-24:2 Days25-26:1 Days27-28: inert pills	days 1-2:0 Days 3-7:2 Days8-24:3 Days25-26:0 Days27-28: inert pills	Monophasic	Monthly

*21-day formulation without inert pills also available.

+Also contains 75 mg ferrous fumarate in pills Days 22-28 or Days 24-28.

‡ Beyaz and Safyral also contain 0.451 mg levomefolate calcium in Days 1-28.

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Table 2- Relative risk of myocardial infarction among current users of hormonal contraceptives from studies in women after 1990.

Authors	year of publication	Year of recruitment	Type of study	Number of women	RR(95% CI)
D'Avanzo et al Case control	1994	1983–1992	Case control	251/475	2.0(0.6–6.7)
Lewis et al.,	1997	1993-1996	Case control	182/635	2.3(1.3–3.9)
WHO Collaborative	1997	1989-1995	Case control	368/941	5.0(2.5–9.9)
Sidney et al	1998	1991-1994	Case control	271/993	0.9(0.4–2.2)
Lidegaard et al	1999	1980-1993	Case control	94/1041	1.4(0.7–2.6)
Dunn et al.,	1999	1993-1995	Case control	448/1728	1.4(0.8–2.5)
Rosenberg et al	2001	1985-1999	Case control	627/2947	1.3(0.8–2.2)
Owen-Smith et al	1998	1994-1995	Cohort	103/309	2.7(0.8–9.0)
Tanis et al	2001	1990-1995	Case control	248/925	2.1(1.4–3.1)
Margolis et al	2007	1991-2002	Cohort	214/48,321	0.7(0.4–1.4)
Gallagher et al	2011	1989–2000	Cohort	494/267,400	2.4(0.6–9.8)

Table 3- Relative risk of myocardial infarction among current users of hormonal contraceptives according to the type of progestincombined with ethinylestradiol.

Authors	year of publication	Year of recruitment	Type of study	Number of women	RR (95% CI)
WHO collaborative1	1996	1989–1993	Case control	141/373	1.5(0.7–3.3)
Heinemann et al	1997	1993-1996	Case control	220/775	2.9(2.0–4.0)
etitti et al	1996	1991-1994	Case control	144/774	0.7(0.3–1.7)
Schwartz et al	1998	1991-1995	Case control	175/1191	0.7(0.3–1.5)
Haapaniemi et al	1997	NA	Case control	140/126	4.2(1.7–10.1)
Lidegaard et al	2002	1994–1998	Case control	626/4054	0.7(0.6–1.0)
Tzourio et al	1995	1990-1993	Case control	72/173	3.1(1.2–8.2)
Kemmeren et al	2002	1990-1995	Case control	203/925	2.1(1.5–3.1)
Siritho et al	2004	1984–1996	Case control	234/234	1.8(0.9–3.6)
Nightingale et al	2004	1992–1998	Nested case control	190/1129	2.3(1.2–4.6)
Martinelli et al	2006	1994–2005	Case control	105/293	2.3(1.4–3.8)
Pezzini et al	2007	NA	Case control	108/216	4.0(2.3–6.8)
Yang et al.,	2009	1991–2004	Cohort	193/45,699	1.1(0.6–2.0)
Gallagher et al	2011a,b	1989–2000	Cohort	699/267,400	0.7(0.5–0.9)

Pooled OR 1.8 (1.2–2.8)

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