ZAGÓRSKI, Karol, SKALSKA-DZIOBEK, Nina, KOZIK, Mateusz, MAŁAGOCKA, Weronika, CHYBOWSKA, Karolina, ORŁOWSKI , Mateusz, NARUSZEWICZ, Maria, MIDRO, Aleksandra and CETNAROWSKI, Przemysław. Metabolic Impacts of Oral Contraceptives A Comprehensive Review of Current Evidence. Quality in Sport. 2024;34:55987 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.34.55987
https://apcz.umk.pl/QS/article/view/55987

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

Metabolic Impacts of Oral Contraceptives: A Comprehensive Review of Current Evidence

Karol Zagórski, Mateusz Kozik, Nina Skalska-Dziobek, Weronika Małagocka, Karolina Chybowska, Mateusz Orłowski, Maria Naruszewicz, Aleksandra Midro, Przemysław Cetnarowski

Abstract

Introduction and objective: Oral hormonal contraception (COC) is a highly popular, as well as extensive group of medications. A significant impact of chronic COC therapy on parameters of lipid metabolism, carbohydrates, binding globulins, coagulation system and body weight of patients has been proven. Given the continuously increasing number of women using COC, initiating therapy at progressively younger ages it is reasonable to investigate the impact of individual medications on patients' organisms completing knowledge with conclusions from newly conducted research, as well as the influence of new types of drugs on the studied indicators.

Material and method: The literature was reviewed in the Pubmed database, GoogleScholar, the positions of the Polish gynecological society with the use of keywords.

State of knowledge: The use of COC is widespread among women. According to the citied studies, over 80% of premenopausal women have declared using oral contraceptives. Typically, COCs consist of a combination of estrogen and progestin components, offering various possible combinations and dosing regimens.

Despite their high efficacy in preventing pregnancy, their impact on lipid and carbohydrate metabolism, as well as consequences remains incompletely understood. Older generations of progestins, due to their similarity to testosterone, can cause negative androgenic effects, while more recent progestins are expected to be neutral.
Summary: Each type of therapy is characterized by individual impact on the patients' organism, however, the majority of progestins affect the increase of triglycerides, HDL and have ambiguous effect on LDL. COC has a limited influence on BMI, carbohydrate metabolism, coagulation system and glycemia.

Keywords: Oral contraceptive, lipids, lipoproteins, carbohydrate metabolism

Introduction

Combined oral contraception (COC), as an integral element of healthcare, plays a crucial role in the lives of contemporary women, enabling fertility control and therapeutic effects, which are especially significant in pathological conditions such as polycystic ovary syndrome (PCOS). COC, being an effective contraceptive method, also demonstrates the ability to regulate the menstrual cycle by inhibiting ovulation and reducing excessive androgen production. In the case of patients presenting endocrine disorders, hyperandrogenism, and metabolic disturbances, COC may contribute to alleviating clinical symptoms by normalizing the levels of sex hormones, improving menstrual cycle regularity, reducing androgenic symptoms, and providing metabolic benefits. Thus, COC not only serves as an effective contraceptive method but also can be an effective therapeutic option, emphasizing its importance in clinical practice and scientific research on women's reproductive health.

Not only are COC notably effective in preventing pregnancies, but it also exerts a broad influence on lipid, lipoprotein and carbohydrate metabolism. Progestins belonging to the first and second generations, including desogestrel, gestodene, norgestimate, levonorgestrel, among others, share structural similarities with testosterone, potentially leading to adverse androgenic effects. Although, newer progestins derived from progesterone or spironolactone, such as cyproterone, chlormadinone, nomegestrol, and drospirenone, are anticipated to cause a more favorable metabolic effect. Estrogens and progestins are able to facilitate insulin secretion, enhance peripheral glucose utilization, promote triglyceride synthesis, increase HDL secretion, and have diverse impacts on LDL cholesterol. On the other hand, progesterone induces insulin resistance and hyperglycemia, mimicking the physiological condition observed during pregnancy. Additionally, progestins have the ability to bind to other receptors such as glucocorticoid, mineralocorticoid, and androgen receptors. Binding to the androgen receptor may lead to weight gain and elevated plasma LDL cholesterol levels. Therapies containing newer progestins like drospirenone and dienogest are known for their anti-androgenic effects. [1]

Cholesterol plays a crucial role in the human body, being an essential component of cell membranes and steroid hormones or bile acids. Various fractions of cholesterol exist, including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Total cholesterol reflects the overall amount of cholesterol in the blood, while HDL is recognized as the "good" cholesterol due to its role in transporting excess cholesterol from tissues to the liver for excretion, thereby contributing to protection against atherosclerosis and heart disease. LDL, known as "bad" cholesterol, transports cholesterol from the liver to the tissues, where it can accumulate in the walls of blood vessels, leading to the formation of atherosclerotic plaques. Conversely, VLDL, serves as primary carrier of triglycerides and plays an important role in lipid metabolism. Understanding the function and importance of the different cholesterol fractions enables the assessment of cardiovascular disease risk and the effectiveness of preventive measures such as oral hormonal contraception.

Plasma triglycerides represent a form of lipids fundamental in the human body, serving as the principal energy reservoir. They consist of three molecules of fatty acids bonded to glycerol, they are stored within adipose cells and released into the bloodstream to provide energy.

However, excess triglycerides in the blood can be harmful and increase the risk of cardiovascular diseases.

Sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG) are two significant protein carriers in the body. SHBG primarily binds to sex hormones such as testosterone and estradiol, regulating their activity and bioavailability in the bloodstream. It plays a crucial role in hormonal balance impacting various physiological processes including sexual development and bone health. Similarly, CBG binds to corticosteroids like cortisol, modulating their distribution and activity. CBG helps regulate the body's response to stress, inflammation, and metabolism. Both SHBG and CBG are essential for maintaining hormonal homeostasis and overall health.

Prothrombin 1+2 and D-dimers are markers of the blood coagulation process, using in the diagnosis of thrombosis and assessment of thrombotic risk in patients. Prothrombin 1+2 is a fragment of prothrombin that undergoes activation during the coagulation process. Its level in serum can be used to monitor the activity of the coagulation system. Conversely, D-dimers are degradation products of blood clots formed during fibrin breakdown. Their presence may indicate the presence of thrombi. Both of these biomarkers are important for assessing thrombotic risk and monitoring anticoagulant therapy in patients with thromboembolic diseases.

The levels of carbohydrate metabolism and Body Mass Index (BMI) are important determinants of metabolic health in the body. Carbohydrate metabolism refers to the process of converting glucose and other carbohydrates into energy essential for cellular and tissue function. Meanwhile, BMI is a measure of the ratio of body weight to height, utilized to assess the degree of obesity or underweight in adults. Elevated BMI levels may correlate with a heightened risk of cardiovascular diseases, type 2 diabetes, and other conditions associated with obesity.

Table 1. Normal ranges of parameters

Parameter	Value
Total cholesterol	114 – 190 mg/dl
HDL cholesterol	> 50 mg/dl
LDL cholesterol	< 115 mg/dl
VLDL cholesterol	< 30 mg/dl
Triglycerides	< 150 mg/dl
SHBG	30 – 90 nmol/l
CBG	19 -45 mg/l
D – dimers	< 500 ug/l
BMI	18,5 – 24,9 kg/m2

Table 2. List of oral contraceptives included in the meta-analysis

Estradiol valerate with dienogest
Ethinylestradiol with levonorgestrel
Ethinylestradiol with drospirenon

Ethinylestradiol with desogestrel
Ethinylestradiol with chlormadinon acetate
Ethinylestradiol with gestoden
Ethinylestradiol with cyproteron acetate
Ethinylestradiol with noretyndron
Medroxyprogesterone acetate
Estetrol with drospirenon

Purpose

The study elucidates the contemporary understanding of the effects of various combinations and doses of combined oral contraceptives, comprehensively assessing the overall impact of each COC on metabolic variables, delineating their influence on lipid and carbohydrate metabolism, BMI, the coagulation system, and binding proteins. The objective was to synthesize existing literature alongside recent reports and studies exploring the ramifications of COC therapy on lipid and carbohydrate metabolism, while assessing potential benefits and risks associated with such supplementation. Adverse events and side effects were duly examined.

Material and methods

A review of the available literature in the Pubmed database, GoogleScholar, in the Via Medica journal database, the positions of the Polish gynecological society was performed. The articles were searched based on keywords “Oral contraceptive”, “lipids”, “lipoproteins”, “cholesterol”, “SHBG”, “carbohydrate metabolism”, The search provided 3173 scientific papers, of which, after rejecting papers that did not meet the authors' criteria, were included 60 research in this paper.

State of knowledge

Cholesterol

The first issue that needs to be checked is influence on cholesterol levels. The thesis of research[2] asserts that the use of combined oral contraceptive modifies the concentrations of total cholesterol, HDL, LDL and triglycerides leading to a marked increase.

Among patients using triphasic levonorgestrel medications, a study[3] revealed reduced levels of HDL cholesterol, meanwhile the results of paper[4] indicate an upward trend in HDL cholesterol, triglycerides, as well as apolipoproteins a1 and a2.

Therapy with oral contraceptives consisting of ethinylestradiol in combination with levonorgestrel, according to eleven sources[5,6,7,8,9,10,11,12,13,14,15] affects a noticeable decrease in serum HDL cholesterol. The drug has an ambiguous effect on LDL cholesterol and VLDL cholesterol, since according to the articles[9,10,11,13,16] their levels increase during treatment, while a decrease in LDL was described in the papers[5,12]. A correlation between the use of ethinylestradiol combined with levonorgestrel and a decrease in total cholesterol was demonstrated in the article[12]. The results[10,17] prove an effect of using medicament on increasing in apolipoprotein B levels, with an additional decrease in apoE and lipoprotein A observed in paper[10]. In addition, the results[18] suggest a weaker increase in HDL and a smaller decrease in LDL during therapy with the combination of ethinylestradiol and levonorgestrel

compared to combinations of ethinylestradiol with drospirenone, desogestrel or cyproterone acetate.

The effects of oral contraceptives containing ethinylestradiol together with drospirenone are not clear. According to studies[19,20], the drug induces a significant increase in total cholesterol, HDL cholesterol and LDL cholesterol, however, the authors[21,22] describe a decrease in triglycerides and cholesterol levels during the use of combined medication as well as therapy containing only drospirenone.

Four papers[23,24,25,26] show the effect of the medication on decreasing LDL increasing HDL. In study[27], metformin was added to the combined ethinylestradiol with drospirenone, resulting in a significant increase in HDL cholesterol.

A study[28] testing a new combined oral contraceptive containing estetrol with drospirenone a limited impact on lipid metabolism was proven.

The influence of drugs containing dienogest on lipid netabolism is inconclusive. According to the authors[5,7], the combination of estradiol with dienogest leads to anincrease in HDL cholesterol and a decrease in LDL, whereas study[6] describes no effect of dienogest on HDL levels in organism, although the source[29] shows a moderate decrease in HDL cholesterol and a minimal increase in LDL. Additionally, according to the article[6], therapy containing dienogest have a marked increase in apolipoprotein A1 levels, while the addition of an estrogenic component induces an increase in apolipoprotein B.

Among participants of ten researches[19,24,25,30,31,32,33,34,35,36] using hormonal contraception containing a combination of ethinylestradiol and desogestrel, an increase in total cholesterol, HDL cholesterol and apolipoproteins was observed, moreover, sources[19,25,32] suggest a simultaneous increase in LDL, while the authors of[31,34] describe a simultaneous decrease in LDL. In addition, three papers[35,37,38] present results suggesting a negligible effect of contraception containing desogestrel on the lipid profile of female patients, at the same time the authors of[22] publish findings showing the effect of desogestrel on reducing total cholesterol, HDL, LDL and triglycerides levels. Oral contraceptives containing gestodene together with ethinylestradiol, according to four studies[15,35,37,38] show minimal influence on the lipid profile of patients. However, results from[4,26,33,34] indicate the specific impact on increasing the levels of HDL cholesterol, triglycerides and apolipoproteins while concurrently reducing LDL cholesterol levels.

According to the article[5], ethinylestradiol combined with chlormadinone acetate increases HDL cholesterol, triglycerides and apolipoproteins A1 and B levels.

Oral contraceptive therapy consisting of ethinylestradiol together with cyproterone acetate, according to two papers[19,39], induces an increase in total cholesterol, HDL cholesterol and LDL cholesterol, however, the authors of the paper[35] made conclusions about the effect of the medication on the increase in HDL cholesterol and the lack of effect on total cholestetol and LDL cholesterol. The therapy containing a combination of ethinylestradiol and norethindrone, according to studies[13,17,40] increases total cholesterol and apolipoprotein levels in patients, with a concomitant increase in LDL cholesterol. Moreover, the source[40] describes a slight decrease in HDL cholesterol.

The outcome of the study[41] is the detection of no impact on lipid metabolism by patients undergoing medroxyprogesterone acetate therapy.

The authors of[3] indicate a positive increase in HDL cholesterol by drugs containing the triphasic norgestimate.
A comparative study[42] on the lipid metabolisms influence in patients using oral contraceptives and patients with a subcutaneous contraceptive implant showed a more significant increase in total cholesterol, HDL, triglycerides during oral medication therapy.
According to the results of the paper[43], the addition of metformin to oral contraceptive therapy does not affect total cholesterol, HDL, LDL, and triglycerides levels compared therapy without metformin.
The result of the study[2] is the conclusion that female patients who are addictive tabacco smokers are distinguished by lower values of lipid parameters compared to non-smoking patients.

Plasma triglycerides
The use of oral contraceptives by female patients very significantly affects the increase triglyceride levels[44]. According to authors[9,11,13,45,46], oral contraceptive therapy with ethinylestradiol and levonorgestrel significantly raises the level of plasma triglycerides, two papers[10,14] describe a very large increase in triglycerides during treatment, while studies[6,12] have not proven any effect of the drug on their levels in patients' organism.
Two sources[6,29] describe a strong correlation between the use of oral contraception based on dienogest and elevated levels of triglycerides in the body.
The result of paper[8] emphasizes a strong influence of medicaments containing desogestrel on the increase in serum triglycerides, meanwhile the authors of study[47] claim that desogestrel has no impact on triglyceride levels, while levonorgestrel reduces them. Authors[19,25,35,36,46] noted a marked increase in triglyceride and phospholipid levels in patients during the use of combination of desogestrel and ethinylestradiol.
In papers[19,35,39,48,49], contraceptive drugs containing cyproterone acetate in combination with ethinylestradiol noticeably increase triglyceride levels and also reduce LDL - C levels.
According to study[18], medicaments containing cyproterone acetate and ethinylestradiol, desogestrel or drospirenone stronger induces an increase in triglyceride levels than preparations consisting of a combination of ethinylestradiol and levonorgestrel.
Three papers[13,17,40] described a clear effect of the combination of ethinylestradiol with noretyndrone on the increase in triglyceride levels.
The results of the study[28], in which new combination of estetrol with drospirenone results in an elevation in lipid parameters, mostly triglyceride levels. Oral contraceptives containing a combination of ethinylestradiol and drospirenone in conducted studies[19,20,25,26] caused a notable increase in triglycerides and apolipoproteins. Moreover, according to the source[21] drospirenone-based medications cause a decrease in triglycerides and cholesterol.
In three papers[26,35,38], a clear rise in triglycerides was observed in women using preparations containing ethinylestradiol in combination with gestodene.

SHBG, CBG
Three papers[18,20,50] noted a significant increase in SHBG and CBG levels during therapy with medicaments containing drospirenone.

According to three studies[18,49,51], combinations of ethinylestradiol and cyproterpne acetate increase SHBG levels in patients' bodies.
Three sources[8,18,52] emphasized the positive effect of desogestrel on SHBG and CBG concentrations, with a 2-4-fold increase highlighted in study[52], and significant increase in carrier proteins - CBG, SHBG, noted during therapy with a combination of desogestrel with ethinylestradiol in paper[31]. According to study[53], medicaments containing desogestrel alone or in combination with ethinylestradiol or estradiol valerate affect a marked increase in CBG.
The highest increase was observed in the dienogest with ethinylestradiol treatment, while source[5] presents the effect of estradiol valerate therapy in combination with dienogest, during which SHBG and CBG levels remained relatively stable.
According to studies[18,45,54], SHBG and CBG parameters significantly increase in ethinylestradiol therapy with levonorgestrel, the results of the paper[18] highlighting a stronger correlation of this therapeutic combination than therapy with drospirenone, desogestrel or cyproterone acetate.
In the paper[3], the positive impact of three-phase norgestimate on SHBG levels was proven.

Prothrombin 1 + 2, D - dimers
In one paper[5], the mean levels of prothrombin 1+2 and D-dimers remained at a similar level during estradiol valerate combined with dienogest therapy.
However, during ethinylestradiol with levonorgestrel treatment, an increase in prothrombin 1+2 levels was observed in two studies[5,11]. In contrast, the effect of therapy on D-dimer levels is inconclusive, as their levels increased during ethinylestradiol combined with levonorgestrel treatment in one study[5] and remained relatively constant in another paper[11]. A study[21] proved that ethinylestradiol can lead to hypercoagulability by inducing various procoagulant factors.

Carbohydrate metabolism
The impact of therapy with ethinylestradiol combined with drospirenone is not clear, as study[20] suggests no change in glucose-insulinemic metabolism, while paper[27] emphasizes a significant increase in the glucose-insulin ratio, meanwhile in article[55] an increase in the insulinogenic index is observed.
According to the authors of papers[8,35,36], patients treated with medicaments containing ethinylestradiol and desogestrel showed no alterations in parameters of insulin sensitivity, glucose, insulin and HbA1c levels, whereas the results of the study[30] pointed towards a notable increase in insulin sensitivity and an enhanced C-peptide response to insulin during therapy.
The effects of treatment with a three-phase combination of ethinylestradiol with norgestimate or gestodene, as described in study[56], led to elevated fasting plasma insulin levels and reduced insulin sensitivity without affecting glucose parameters. In contrast, a study[37] showed a positive impact on glucose and insulin responses of a gestodene combined with ethinylestradiol. On the other hand, the results of paper[35] document a negligible effect of the drug on glucose, insulin and HbA1c levels in the body.
Source[30] describes the influence of ethinylestradiol in combination with chlormadinone acetate on increasing the C-peptide response to glucose and insulin.

According to studies[39,49], a drug containing a combination of ethinylestradiol and cyproterone acetate increases insulin and glucose levels in the OGTT test, while papers[19,35,] demonstrate a minimal impact of the drug on glucose, insulin and HbA1c levels in patients' organism.
Authors[5,9], noted that therapy with a combination of ethinylestradiol and levonorgestrel resulted in heightened carbohydrate metabolism, increased levels of insulin and C-peptide as well as decreased glucose levels.
In study[5], a negligible effects of estradiol valerate along with dienogest on carbohydrate metabolism was described. No changes in carbohydrate metabolism were reported among patients treated with medroxyprogesterone acetate, as per[41].

BMI

According to the authors of studies[27,57,], the use of combined therapy with ethinylestradiol and drospirenone does not result in changes in clinical measurements of body weight, BMI or WHR. However, source[57] indicates an increase in adipose tissue mass with a sustained BMI value. In contrast, the article[23] highlights a noticeable reduction in BMI in the group treated with ethinylestradiol and drospirenone. Additionally, the paper[28] indicates minimal changes in body weight during therapy with a new contraceptive containing estetrol in combination with drospirenone.
A study[19] showed no impact of cyproterone acetate therapy on BMI. According to source[5], treatment with ethinylestradiol in combination with levonorgestrel does not significantly affect the BMI level of patients, while a medicament containing estradiol valerate and dienogest does not affect BMI index.
The results from study[42] revealed a clear increase in body weight and BMI in patients treated with combined contraceptives and subcutaneous contraceptive implants. The results of four studies[43,58,59,60,], in which a metformin dose was added to combined contraceptives therapy, indicated a significant decrease in glucose levels, improvement in insulin sensitivity, induction of weight loss, as well as BMI reduction in patients, thus positively influencing the course of treatment.

Discussion and conclusion

According to the cited studies, the analysis of the effects of routine use of combined oral hormonal contraception (COC) on lipid metabolism, carbohydrate metabolism, BMI, and other metabolic parameters demonstrates their significant impact on the body.
With the emergence of new combinations, doses, and administration methods, the risk-benefit profile associated with COC has significantly evolved. The metabolic effects of third and fourth generation progestins, particularly when combined with natural estrogens, appear to be minimal. Newer generations of progestins are essentially devoid of androgenic, estrogenic, or glucocorticoid-related side effects, leading to an improved safety profile.
The impact on the patient's body varies depending on the specific COC variant. The latest generation of COCs demonstrate a more favorable effect on patients, with lesser deregulation

of lipid and carbohydrate metabolism. Additionally, significant improvements in metabolic parameters have been observed with the addition of metformin to COC therapy.
However, the collected information does not fully elucidate the overall impact of combined oral hormonal contraceptive therapy on the body. Further research is needed to explore the use of COCs among women for fertility regulation purposes, as well as for the management of chronic conditions such as polycystic ovary syndrome

Disclosures

Author contribution: Conceptulization: Karol Zagórski and Mateusz Kozik; ***methodology:*** Nina Skalska-Dziobek; ***software:*** Weronika Małagocka; ***check:*** Karolina Chybowska, Mateusz Orłowski; ***formal analysis:*** Maria Naruszewicz; ***investigation:*** Aleksandra Midro; ***resources:*** Przemysław Cetnarowski; ***data curation:*** Nina Skalska-Dziobek; ***writing – rough preparation:*** Karol Zagórski; ***writing – review and editing:*** Mateusz Kozik, Weronika Małagocka, Karolina Chybowska; ***visualization:*** Mateusz Orłowski, Przemysław Cetrnarowski; ***supervision:*** Maria Naruszewicz; ***project administration:*** Aleksandra Midro.

All authors have read and agreed with the final, published version of the manuscript.

Funding statement:
No external funding was received to perform this review.

Institutional Review Board Statement:
Not applicable – this review included analysis of the available literature.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

Conflict of interest:
The authors declare no conflict of interest.

References

1. Silva-Bermudez LS, Toloza FJK, Perez-Matos MC, de Souza RJ, Banfield L, Vargas-Villanueva A, Mendivil CO. Effects of oral contraceptives on metabolic parameters in

adult premenopausal women: a meta-analysis. Endocr Connect. 2020 Oct;9(10):978-998. doi: 10.1530/EC-20-0423. PMID: 33048062; PMCID: PMC7576645.

2. Campesi I, Montella A, Sotgiu G, Saderi L, Tonolo G, Seghieri G, Franconi F. Smoking and combined oral contraceptives should be considered as an independent variable in sex and gender-oriented studies. Toxicol Appl Pharmacol. 2022 Dec 15;457:116321. doi: 10.1016/j.taap.2022.116321. Epub 2022 Nov 22. PMID: 36423693.
3. Janaud A, Rouffy J, Upmalis D, Dain MP. A comparison study of lipid and androgen metabolism with triphasic oral contraceptive formulations containing norgestimate or levonorgestrel. Acta Obstet Gynecol Scand Suppl. 1992;156:33-8. doi: 10.3109/00016349209156513. PMID: 1324555.
4. Steinmetz A, Bauer K, Jürgensen R, Kaffarnik H. Low-dose oral contraceptives lower plasma levels of apolipoprotein E. Eur J Obstet Gynecol Reprod Biol. 1990 Nov;37(2):155-62. doi: 10.1016/0028-2243(90)90108-d. PMID: 2147014.
5. Junge W, Mellinger U, Parke S, Serrani M. Metabolic and haemostatic effects of estradiol valerate/dienogest, a novel oral contraceptive: a randomized, open-label, single-centre study. Clin Drug Investig. 2011;31(8):573-584. doi: 10.2165/11590220-000000000-00000. PMID: 21721593.
6. Wiegratz I, Lee JH, Kutschera E, Bauer HH, von Hayn C, Moore C, Mellinger U, Winkler UH, Gross W, Kuhl H. Effect of dienogest-containing oral contraceptives on lipid metabolism. Contraception. 2002 Mar;65(3):223-9. doi: 10.1016/s0010-7824(01)00310-9. PMID: 11929644.
7. Shahnazi M, Farshbaf-Khalili A, Pourzeinali-Beilankouh S, Sadrimehr F. Effects of Second and Third Generation Oral Contraceptives on Lipid and Carbohydrate Metabolism in Overweight and Obese Women: A Randomized Triple-Blind Controlled Trial. Iran Red Crescent Med J. 2016 Jun 19;18(9):e36982. doi: 10.5812/ircmj.36982. PMID: 28144464; PMCID: PMC5253509.
8. Song S, Chen JK, Yang PJ, He ML, Li LM, Fan BC, Rekers H, Fotherby K. A cross-over study of three oral contraceptives containing ethinyloestradiol and either desogestrel or levonorgestrel. Contraception. 1992 Jun;45(6):523-32. doi: 10.1016/0010-7824(92)90103-z. PMID: 1535580.
9. Skouby SO, Endrikat J, Düsterberg B, Schmidt W, Gerlinger C, Wessel J, Goldstein H, Jespersen J. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 microg ethinyl estradiol combined with 100 microg levonorgestrel. Contraception. 2005 Feb;71(2):111-7. doi: 10.1016/j.contraception.2004.08.017. PMID: 15707560.
10. Scharnagl H, Petersen G, Nauck M, Teichmann AT, Wieland H, März W. Double-blind, randomized study comparing the effects of two monophasic oral contraceptives containing ethinylestradiol (20 microg or 30 microg) and levonorgestrel (100 microg or 150 microg) on lipoprotein metabolism. Contraception. 2004 Feb;69(2):105-13. doi: 10.1016/j.contraception.2003.10.004. PMID: 14759614.

11. Endrikat J, Klipping C, Cronin M, Gerlinger C, Ruebig A, Schmidt W, Düsterberg B. An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 microg ethinyl estradiol and 100 microg levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables. Contraception. 2002 Mar;65(3):215-21. doi: 10.1016/s0010-7824(01)00316-x. PMID: 11929643.
12. Loke DF, Ng CS, Samsioe G, Holck S, Ratnam SS. A comparative study of the effects of a monophasic and a triphasic oral contraceptive containing ethinyl estradiol and levonorgestrel on lipid and lipoprotein metabolism. Contraception. 1990 Nov;42(5):535-54. doi: 10.1016/0010-7824(90)90081-6. PMID: 2125546.
13. Notelovitz M, Feldman EB, Gillespy M, Gudat J. Lipid and lipoprotein changes in women taking low-dose, triphasic oral contraceptives: a controlled, comparative, 12-month clinical trial. Am J Obstet Gynecol. 1989 May;160(5 Pt 2):1269-80. doi: 10.1016/s0002-9378(89)80012-2. PMID: 2655452.
14. Larsson-Cohn U, Wallentin L, Zador G. Plasma lipids and high density lipoproteins during oral contraception with different combinations of ethinyl estradiol and levonorgestrel. Horm Metab Res. 1979 Jul;11(7):437-40. doi: 10.1055/s-0028-1092755. PMID: 225252.
15. Kjaer A, Lebech AM, Borggaard B, Refn H, Pedersen LR, Schierup L, Bremmelgaard A. Lipid metabolism and coagulation of two contraceptives: correlation to serum concentrations of levonorgestrel and gestodene. Contraception. 1989 Dec;40(6):665-73. doi: 10.1016/0010-7824(89)90070-x. PMID: 2515940.
16. Flores-Rodriguez A, Diaz Gonzalez-Colmenero F, Garcia-Leal M, Saenz-Flores M, Burciaga-Jimenez E, Zuñiga-Hernandez JA, Alvarez-Villalobos NA, Rodríguez-Guajardo R, Morales-Martinez FA, Sordia-Hernandez LH, Rodriguez-Gutierrez R. Harms of third- and fourth-generation combined oral contraceptives in premenopausal women: A systematic review and meta-analysis. J Investig Med. 2023 Dec;71(8):871-888. doi: 10.1177/10815589231184227. Epub 2023 Jul 6. PMID: 37415461.
17. Kakis G, Powell M, Marshall A, Woutersz TB, Steiner G. A two-year clinical study of the effects of two triphasic oral contraceptives on plasma lipids. Int J Fertil Menopausal Stud. 1994 Sep-Oct;39(5):283-91. PMID: 7820162.
18. Amiri M, Nahidi F, Bidhendi-Yarandi R, Khalili D, Tohidi M, Ramezani Tehrani F. A comparison of the effects of oral contraceptives on the clinical and biochemical manifestations of polycystic ovary syndrome: a crossover randomized controlled trial. Hum Reprod. 2020 Jan 1;35(1):175-186. doi: 10.1093/humrep/dez255. PMID: 31916574
19. Amiri M, Ramezani Tehrani F, Nahidi F, Kabir A, Azizi F, Carmina E. Effects of oral contraceptives on metabolic profile in women with polycystic ovary syndrome: A meta-analysis comparing products containing cyproterone acetate with third generation progestins. Metabolism. 2017 Aug;73:22-35. doi: 10.1016/j.metabol.2017.05.001. Epub 2017 May 10. PMID: 28732568
20. Romualdi D, De Cicco S, Busacca M, Gagliano D, Lanzone A, Guido M. Clinical efficacy and metabolic impact of two different dosages of ethinyl-estradiol in association with drospirenone in normal-weight women with polycystic ovary

syndrome: a randomized study. J Endocrinol Invest. 2013 Sep;36(8):636-41. doi: 10.1007/BF03346756. PMID: 24105072.
21. Regidor PA, Mueller A, Mayr M. Pharmacological and metabolic effects of drospirenone as a progestin-only pill compared to combined formulations with estrogen. Womens Health (Lond). 2023 Jan-Dec;19:17455057221147388. doi: 10.1177/17455057221147388. PMID: 36744531; PMCID: PMC9905034.
22. Palacios S, Colli E, Regidor PA. Metabolic and laboratory effects of a progestin-only pill containing drospirenone 4 mg in comparison to desogestrel 75 µg: a double-blind, double-dummy, prospective, randomised study. Eur J Contracept Reprod Health Care. 2021 Dec;26(6):454-461. doi: 10.1080/13625187.2021.1957094. Epub 2021 Aug 4. PMID: 34348526.
23. Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception. 2010 Aug;82(2):139-46. doi: 10.1016/j.contraception.2010.02.009. Epub 2010 May 23. PMID: 20654754.
24. Klipping C, Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism. Contraception. 2005 Jun;71(6):409-16. doi: 10.1016/j.contraception.2004.12.005. PMID: 15914128.
25. Gaspard U, Endrikat J, Desager JP, Buicu C, Gerlinger C, Heithecker R. A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. Contraception. 2004 Apr;69(4):271-8. doi: 10.1016/j.contraception.2003.11.003. PMID: 15033400.
26. Yildizhan R, Yildizhan B, Adali E, Yoruk P, Birol F, Suer N. Effects of two combined oral contraceptives containing ethinyl estradiol 30 microg combined with either gestodene or drospirenone on hemostatic parameters, lipid profiles and blood pressure. Arch Gynecol Obstet. 2009 Aug;280(2):255-61. doi: 10.1007/s00404-008-0907-x. Epub 2009 Jan 6. PMID: 19125264.
27. Fruzzetti F, Perini D, Lazzarini V, Parrini D, Gambacciani M, Genazzani AR. Comparison of effects of 3 mg drospirenone plus 20 µg ethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. Fertil Steril. 2010 Oct;94(5):1793-8. doi: 10.1016/j.fertnstert.2009.10.016. PMID: 19931080.
28. Gemzell-Danielsson K, Cagnacci A, Chabbert-Buffet N, Douxfils J, Foidart JM, Kubba A, Lete Lasa LI, Mansour D, Neulen J, Neves J, Palma F, Römer T, Spaczyński R, Tóth V. A novel estetrol-containing combined oral contraceptive: European expert panel review. Eur J Contracept Reprod Health Care. 2022 Oct;27(5):373-383. doi: 10.1080/13625187.2022.2093850. Epub 2022 Jul 21. PMID: 35862627.

29. Köhler G, Göretzlehner G, Brachmann K. Lipid metabolism during treatment of endometriosis with the progestin dienogest. Acta Obstet Gynecol Scand. 1989;68(7):633-5. doi: 10.3109/00016348909013283. PMID: 2631529.
30. Cagnacci A, Ferrari S, Tirelli A, Zanin R, Volpe A. Insulin sensitivity and lipid metabolism with oral contraceptives containing chlormadinone acetate or desogestrel: a randomized trial. Contraception. 2009 Feb;79(2):111-6. doi: 10.1016/j.contraception.2008.09.002. Epub 2008 Oct 16. PMID: 19135567.
31. van den Ende A, Geurts TB, Kloosterboer HJ. A randomized cross-over study comparing pharmacodynamic and metabolic variables of a new combiphasic and a well-established triphasic oral contraceptive. Eur J Contracept Reprod Health Care. 1997 Sep;2(3):173-80. doi: 10.3109/13625189709167473. PMID: 9678089.
32. Petersen KR, Skouby SO, Pedersen RG. Desogestrel and gestodene in oral contraceptives: 12 months' assessment of carbohydrate and lipoprotein metabolism. Obstet Gynecol. 1991 Oct;78(4):666-72. PMID: 1833682.
33. Gevers Leuven JA, Dersjant-Roorda MC, Helmerhorst FM, de Boer R, Neymeyer-Leloux A, Havekes L. Estrogenic effect of gestodene- or desogestrel-containing oral contraceptives on lipoprotein metabolism. Am J Obstet Gynecol. 1990 Jul;163(1 Pt 2):358-62. doi: 10.1016/0002-9378(90)90582-r. PMID: 2142575.

34. Bertolini S, Elicio N, Cordera R, Gapitanio GL, Montagna G, Croce S, Saturnino M, Balestreri R, De Cecco L. Effects of three low-dose oral contraceptive formulations on lipid metabolism. Acta Obstet Gynecol Scand. 1987;66(4):327-32. doi: 10.3109/00016348709103647. PMID: 2962417.
35. Miccoli R, Orlandi MC, Fruzzetti F, Giampietro O, Melis G, Ricci C, Bertolotto A, Fioretti P, Navalesi R. Metabolic effects of three new low-dose pills: a six-month experience. Contraception. 1989 Jun;39(6):643-52. doi: 10.1016/0010-7824(89)90039-5. PMID: 2526717.
36. Cagnacci A, Ferrari S, Tirelli A, Zanin R, Volpe A. Route of administration of contraceptives containing desogestrel/etonorgestrel and insulin sensitivity: a prospective randomized study. Contraception. 2009 Jul;80(1):34-9. doi: 10.1016/j.contraception.2009.01.012. Epub 2009 Mar 17. PMID: 19501213.
37. van der Mooren MJ, Klipping C, van Aken B, Helmerhorst E, Spielmann D, Kluft C. A comparative study of the effects of gestodene 60 microg/ethinylestradiol 15 microg and desogestrel 150 microg/ethinylestradiol 20 microg on hemostatic balance, blood lipid levels and carbohydrate metabolism. Eur J Contracept Reprod Health Care. 1999 Nov;4 Suppl 2:27-35. doi: 10.3109/13625189909085267. PMID: 14677622.
38. März W, Jung-Hoffmann C, Heidt F, Gross W, Kuhl H. Changes in lipid metabolism during 12 months of treatment with two oral contraceptives containing 30 micrograms ethinylestradiol and 75 micrograms gestodene or 150 micrograms desogestrel. Contraception. 1990 Mar;41(3):245-58. doi: 10.1016/0010-7824(90)90066-5. PMID: 2138973.
39. Vexiau P, Vexiau-Robert D, Martineau I, Hardy N, Villette JM, Fiet J, Cathelineau G. Metabolic effect at six and twelve months of cyproterone acetate (2 mg) combined

with ethinyl estradiol (35 micrograms) in 31 patients. Horm Metab Res. 1990 Apr;22(4):241-5. doi: 10.1055/s-2007-1004893. PMID: 2141001.
40. Patsch W, Brown SA, Gotto AM Jr, Young RL. The effect of triphasic oral contraceptives on plasma lipids and lipoproteins. Am J Obstet Gynecol. 1989 Nov;161(5):1396-401. doi: 10.1016/0002-9378(89)90703-5. PMID: 2686455.
41. Ozdemir S, Görkemli H, Gezginç K, Ozdemir M, Kiyici A. Clinical and metabolic effects of medroxyprogesterone acetate and ethinyl estradiol plus drospirenone in women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2008 Oct;103(1):44-9. doi: 10.1016/j.ijgo.2008.05.017. Epub 2008 Jul 16. PMID: 18635183.
42. Giraudo F, Salinas A, Merino PM, Iñiguez G, López P, Castro A, Lardone MC, Cavada G, Cassorla F, Codner E. Subdermal Progestin Implant and an Oral Combined Hormonal Contraceptive in Youth with Type 1 Diabetes. J Pediatr Adolesc Gynecol. 2023 Nov 25:S1083-3188(23)00449-7. doi: 10.1016/j.jpag.2023.11.009. Epub ahead of print. PMID: 38012981
43. Wu L, Liu Y, Huang X, Lin K, Liu Y, Li Z, Wei T, Song L, Hua Y, Wang X. Oral contraceptives (OCs) in combination with metformin versus OCs alone on metabolism in nonobese polycystic ovary syndrome: A meta-analysis and systematic review of randomized controlled trials. Clin Endocrinol (Oxf). 2023 Jul;99(1):3-16. doi: 10.1111/cen.14895. Epub 2023 Apr 7. PMID: 36799083.
44. Maeda E, Koshiba A, Mori T, Ito F, Kataoka H, Okimura H, Sugahara T, Tarumi Y, Kusuki I, Khan KN, Kitawaki J. Atherosclerosis-related biomarkers in women with endometriosis: The effects of dienogest and oral contraceptive therapy. Eur J Obstet Gynecol Reprod Biol X. 2020 Apr 23;7:100108. doi: 10.1016/j.eurox.2020.100108. PMID: 32715291; PMCID: PMC7379146.
45. Larsson-Cohn U, Fåhraeus L, Wallentin L, Zador G. Effects of the estrogenicity of levonorgestrel/ethinylestradiol combinations of the lipoprotein status. Acta Obstet Gynecol Scand Suppl. 1982;105:37-40. doi: 10.3109/00016348209155316. PMID: 6805243.
46. März W, Gross W, Gahn G, Romberg G, Taubert HD, Kuhl H. A randomized crossover comparison of two low-dose contraceptives: effects on serum lipids and lipoproteins. Am J Obstet Gynecol. 1985 Oct 1;153(3):287-93. doi: 10.1016/s0002-9378(85)80114-9. PMID: 2931988.
47. Kauppinen-Mäkelin R, Kuusi T, Ylikorkala O, Tikkanen MJ. Contraceptives containing desogestrel or levonorgestrel have different effects on serum lipoproteins and post-heparin plasma lipase activities. Clin Endocrinol (Oxf). 1992 Feb;36(2):203-9. doi: 10.1111/j.1365-2265.1992.tb00959.x. PMID: 1533186.
48. Mhao NS, Al-Hilli AS, Hadi NR, Jamil DA, Al-Aubaidy HA. A comparative study to illustrate the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome. Diabetes Metab Syndr. 2016 Jan-Mar;10(1 Suppl 1):S95-8. doi: 10.1016/j.dsx.2015.10.001. Epub 2015 Nov 12. PMID: 26703220.
49. Teede HJ, Meyer C, Hutchison SK, Zoungas S, McGrath BP, Moran LJ. Endothelial function and insulin resistance in polycystic ovary syndrome: the effects of medical

therapy. Fertil Steril. 2010 Jan;93(1):184-91. doi: 10.1016/j.fertnstert.2008.09.034. Epub 2008 Nov 18. PMID: 19019358.
50. Klipping C, Duijkers I, Mawet M, Maillard C, Bastidas A, Jost M, Foidart JM. Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone. Contraception. 2021 Apr;103(4):213-221. doi: 10.1016/j.contraception.2021.01.001. Epub 2021 Jan 9. PMID: 33428907.
51. Vermeulen A, Rubens R. Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. Contraception. 1988 Oct;38(4):419-28. doi: 10.1016/0010-7824(88)90083-2. PMID: 2974791
52. Cachrimanidou AC, Hellberg D, Nilsson S, von Schoulz B, Crona N, Siegbahn A. Hemostasis profile and lipid metabolism with long-interval use of a desogestrel-containing oral contraceptive. Contraception. 1994 Aug;50(2):153-65. doi: 10.1016/0010-7824(94)90051-5. PMID: 7956214.
53. Kangasniemi MH, Arffman RK, Haverinen A, Luiro K, Hustad S, Heikinheimo O, Tapanainen JS, Piltonen TT. Effects of estradiol- and ethinylestradiol-based contraceptives on adrenal steroids: A randomized trial. Contraception. 2022 Dec;116:59-65. doi: 10.1016/j.contraception.2022.08.009. Epub 2022 Sep 7. PMID: 36084710.

54. Ågren UM, Anttila M, Mäenpää-Liukko K, Rantala ML, Rautiainen H, Sommer WF, Mommers E. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol in comparison to one containing levonorgestrel and ethinylestradiol on markers of endocrine function. Eur J Contracept Reprod Health Care. 2011 Dec;16(6):458-67. doi: 10.3109/13625187.2011.614363. Epub 2011 Sep 26. PMID: 21942708; PMCID: PMC3233273.
55. Battaglia C, Mancini F, Fabbri R, Persico N, Busacchi P, Facchinetti F, Venturoli S. Polycystic ovary syndrome and cardiovascular risk in young patients treated with drospirenone-ethinylestradiol or contraceptive vaginal ring. A prospective, randomized, pilot study. Fertil Steril. 2010 Sep;94(4):1417-1425. doi: 10.1016/j.fertnstert.2009.05.044. Epub 2009 Jul 9. PMID: 19591981.
56. Petersen KR, Christiansen E, Madsbad S, Skouby SO, Andersen LF, Jespersen J. Metabolic and fibrinolytic response to changed insulin sensitivity in users of oral contraceptives. Contraception. 1999 Dec;60(6):337-44. doi: 10.1016/s0010-7824(99)00107-9. PMID: 10715368.
57. Aydin K, Cinar N, Aksoy DY, Bozdag G, Yildiz BO. Body composition in lean women with polycystic ovary syndrome: effect of ethinyl estradiol and drospirenone combination. Contraception. 2013 Mar;87(3):358-62. doi: 10.1016/j.contraception.2012.07.005. Epub 2012 Aug 13. PMID: 22898361.
58. Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. Hum Reprod. 2002 Jul;17(7):1729-37. doi: 10.1093/humrep/17.7.1729. PMID: 12093831.

59. Feng W, Jia YY, Zhang DY, Shi HR. Management of polycystic ovarian syndrome with Diane-35 or Diane-35 plus metformin. Gynecol Endocrinol. 2016;32(2):147-50. doi: 10.3109/09513590.2015.1101441. Epub 2015 Oct 28. PMID: 26507097
60. Song J, Ruan X, Gu M, Wang L, Wang H, Mueck AO. Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. Gynecol Endocrinol. 2018 May;34(5):413-417. doi: 10.1080/09513590.2017.1407752. Epub 2017 Nov 24. PMID: 29172796.