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## The influence of combined oral contraceptive pills on carbohydrate metabolism in healthy women and in women with PCOS - a systemic review

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### Abstract

Introduction: Combined oral contraceptives (COCs) are a commonly used contraceptive method. They are used as one of the method therapy in women with PCOS. Outcomes from previous studies about the influence of the COCs on carbohydrate metabolism are diverse. Purpose: To assess the influence of combined oral contraceptives on parameters of carbohydrate metabolism in healthy women and in women with PCOS.

Review methods: We conducted a systemic review according to PRISMA protocol. Databases as Pubmed, Scopus, Web of Science were screened systematically. The inclusion criteria were: a study published in 2016-2021, which contains information about the change of carbohydrate parameters as: fasting insulin, fasting glucose levels; HOMA-IR; insulin, glucose levels etc. The participants were healthy/PCOS women. Studies conducted on animals were excluded. The final number of studies enrolled in this study is 15.

Abbreviated description of the state of knowledge: There are studies in which negative influences of the COCs on carbohydrate metabolism are proved. Nevertheless, many of these studies were conducted years ago. COCs, when they were introduced in 1960s, contained different compounds and amounts of hormones. Over the years a successive decrease in estrogen dose has occurred. Also progestogens have been developed in order to minimize the androgenic effects. Results of studies conducted nowadays are ambiguous.

Summary: A significant impairment of carbohydrate metabolism in short period of time was not detected in healthy women. In women with PCOS the results depended on the type of COCs used.

**Key words were found by MeSH browser and included terms as: Hormonal Contraception; Contraceptives oral combined; Glucose Metabolism Disorders; Insulin Resistance; Glucose Intolerance.**

## 1. Introduction:

In almost every part of the world the majority of women in reproductive age reaches for one or more contraception methods. Among the population of European women the contraception use reaches up to approximately 70%. There are many benefits of contraception use, for instance: preventing maternal morbidity and mortality, reducing adolescent pregnancies and unsafe abortion from unintended pregnancies, also preventing from HIV/AIDS [1].

Oral contraception is across the world one of the most common method chosen to prevent from unintended pregnancies. In 2019 this method was used by 150 million women all over the world [2].

Currently, there are three types of oral contraceptive pills: combined estrogen-progesterone, progesterone-only, and continuous or extended use pill [3]. The use of COCs extends far beyond contraception. The advantages of using COCs remain as above: they protect against symptomatic pelvic inflammatory, cancer of the ovary and cancer of the lining of the uterus. Also they may protect against ovarian cysts and iron-deficiency anemia. Last but not least, COCs may significantly reduce menstrual bleeding problems and symptoms of polycystic ovary syndrome [4].

That information is the evidence that there is a high prevalence of the COC use among the woman across the world, therefore it is a significant matter to assess potential health risk of the COC therapy. Since the introduction of COCs in 1960 there are plenty researches going on that take into consideration different purposes of using COCs than a prevention from pregnancy, this includes examining the influence on the metabolism of carbohydrates and fats [5],[6].

Some results suggest that estrogen causes insulin resistance, while progestins modify the response. According to the research of Wynn Institute for Metabolic Research from 1992, estrogen causes insulin resistance, while progestins modify the response. Levonorgestrel

combinations may increase the second phase pancreatic insulin secretion but does not affect the insulin's half-period. In contrast to this, a desogestrel combination may increase the insulin half-period but does not affect insulin secretion. This study shows no effect on insulin resistance by progestin-only formulation [7]. A different research from 1979 proves that use of COCs containing 75ug or more of estrogen can lead to abnormal insulin response to glucose [8]. A study conducted by O. Skouby in 1987 shows that use of COCs is associated with lower insulin sensitivity, but not with any disorder of glucose intolerance [9]. Noteworthy is the fact that the dose of estrogen in COCs was steadily decreased during the years.. In 1960s, the high-dose oral contraceptives containing >50 ILg of estrogen; in 1970s there were medium-dose oral contraceptives containing 50 ILg of estrogen; and in 1980s there were the low-dose oral contraceptives containing <50ug of estrogen [10]. Older COCs contained a more androgenic progesterone component comparing to the COCs used nowadays which are not only less androgenic but also some of them present anti-androgenic effect [11].

The prevalence of diabetic mellitus is increasing and according to some researches by the 2030 it will have increased by 54% among American society [12]. Some complications related to diabetes, including cardiovascular disease, kidney disease, neuropathy, blindness, and lower-extremity amputation, are a significant cause of increased morbidity and mortality among people with diabetes [13]. Prediabetic states characterized by an impaired fasting glucose level or impaired glucose tolerance can easy lead to diabetes mellitus [14]. Minding the health complications of diabetes mellitus it is a priority to assess, determine and subsequently reduce the factors that cause carbohydrate metabolism disorders.

Polycystic ovary syndrome is a disease that is strongly associated with T2DM and insulin resistance. Affected women struggle with many problems, for instance hirsutism and reduced fertility. One of them is also insulin resistance. The mechanism of its origin in PCOS is associated with an increased degree of phosphorylation of serine kinases and the insulin receptor. Insulin acts as a gonadotropin-like hormone by stimulating the ovary to steroidogenesis. It is associated with weight gain and the disturbance of the menstrual cycle [15]. One way to reduce androgenization and to achieve cycle recovery is to administer oral contraceptives. They also affect the sugar management of women with PCOS. In women with PCOS there is impaired compensatory insulin secretion. This leads to insulin resistance. Glucose intolerance in the PCOS group is caused by a decreased beta-cell response in the face of an increased need for factors enhancing insulin resistance.

**Purpose:** In this research we tried to find an answer to how new COCs used nowadays influence carbohydrate metabolism in healthy women and in women with PCOS. We took under consideration results from researches publicated in the last 5 years (2016-2021) in aim to focus only on the newest research outcomes.

## 2. Material and methods:

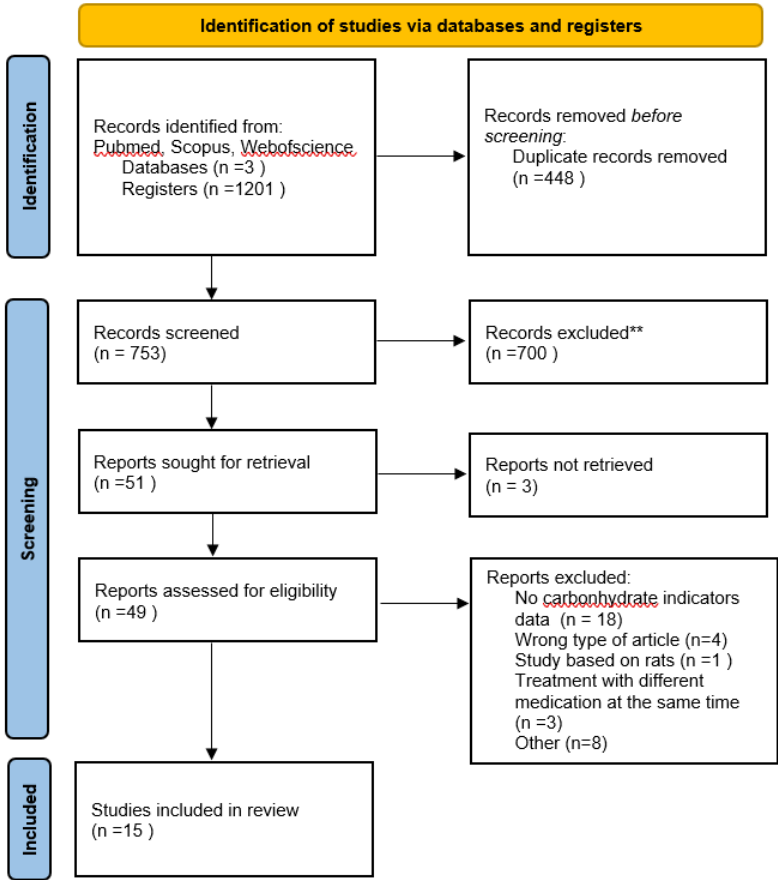
We conducted a systemic review according to PRISMA protocol. Databases as Pubmed, Scopus and Web of Science were screened systematically. The aim of our research was to find articles published in 2016-2021 that were about the influence of the combined oral contraceptives on carbohydrate metabolism in healthy women and in women with PCOS. We used PICO method to conduct this study.

Searching process is shown in a chart below. Authors of this study were screening titles and abstracts independently of each other. The inclusion criteria were: a study published in 2016-2021, in which there was such information about the carbohydrate parameters among patients as: fasting insulin, fasting glucose, HOMA-IR, Insulin, Glucose, HbA1, C-peptide. The participants were healthy women or women with PCOS. Studies conducted on animals were excluded. We eliminated duplicates and after that 753 articles were left. On the basis of screened abstracts and titles we included to further analysis 49 articles which we fully read. Only clinical cohort studies and randomized controlled trials were included in this review. The final number of studies enrolled in this study is 15.

Figure 1. Prisma flow diagram

Results:

3. Influence of the COCs on carbohydrate meabolism in healthy women



So far, many researches were conducted with the aim to answer the question whether there is any connection between COC use and carbohydrate metabolism disorders. Outcomes of these studies are ambiguous.

3.1 Lack of influence of the COCs on carbohydrate metabolism in healthy women

Some medical studies have shown no effect of COCs on fasting glucose and fasting insulin levels. Slight differences in fasting glucose level, HOMA-IR, ISI0 were not statistically significant [16], [17], [18]. In other studies there were no significant differences in the OGTT results between the groups. To sum up, the negative influence of COCs on carbohydrate metabolism was not proven [19]. The result of a study based on data from NFBCand YFS and

FINRISK shows that in both groups (COC starters and COC stoppers) no significant changes in carbohydrate metabolism parameters were observed, whereas in persistent COC users there were only slight metabolic changes compared to participants that did not use any COCs during a 6-year follow-up. Long-term data analysis proves that metabolic changes occur at baseline and at the end point of COC use. Nevertheless, the long-term COC use does not seem to cause any accumulated negative metabolic effects [20].

### 1.1 Negative influence of the COCs on carbohydrate metabolism in healthy women

Outcomes observed in a study based on data from population-based Northern Finland Birth Cohort 1966. In a group of COC users for more than 5 years there was a higher risk of preDM and T2DM compared to a group of nonhormonal contraceptive users for more than 5 years [21].

A connection between time and the negative influence of COC use is shown also by the results of a clinical trial consisting of 55 women from Saudi Arabia. Glucose levels were significantly higher in COC users compared to non-users. The highest glucose level was observed in women taking COCs for the longest period of time (5-7 years) [22].

Outcomes from the above-mentioned studies did not explicitly determine whether the use of COCs can lead to carbohydrate metabolism disorders. The majority of studies was based on a small amount of participants and had a short duration of follow-ups, which is undoubtedly a weakness of these researches. On the basis of these studies it can be assumed that longer time of COC use is bonded with a higher risk of carbohydrate metabolism disorders and that side effects can be delayed. Nevertheless, more studies with a larger amount of participants and longer follow-ups are necessary to draw accurate conclusions about the influence of COCs on carbohydrate metabolism disorders.

## 2. Influence of the COCs on carbohydrate metabolism in women with PCOS:

### 2.1 Polycystic ovary syndrome

COC are one of the most often used treatment for polycystic ovary syndrome. [23] In this research we tried to answer the question whether the COC therapy can worsen carbohydrate metabolism and thus lead to insulin resistance.

### 2.2 Positive influence of the COCs on carbohydrate metabolism in women with PCOS

The increased risk of hypoglycemia during the combined metformin and COC therapy might be associated with an increased insulin release. The COC use caused the HOMA-IR, insulin, glucose levels decrease and improved the OGTT. However, it's the combined therapy of COCs and metformin that obtained significantly greater influence- it lowered HOMA-IR and improved OGTT [24]. Another randomized prospective trial showed that COCs containing drospirenone has a positive influence on the glucose metabolism profiles. HOMA-IR decreased [25]. Some COC treatments show that HOMA-IR and a insulin resistance index also decreased which indicates that COCs have a positive influence on carbohydrate metabolism in women with PCOS [26], [27].

### 2.3 Negative influence of the COCs on carbohydrate metabolism in women with PCOS

In some researches a deterioration of glucose tolerance in women using COCs was observed. One of the examples is a study where women involved in it suffered from insulin resistance

(associated with their PCOS) that was deteriorated by the COCs. It seems that the crucial factor was the insulinogenic index of beta cell function. These cells after a 3-month therapy showed a significant impairment of insulin secretion. Because of that a deterioration of glucose tolerance in women with PCOS using COCs was observed.

Some results showed that COC therapy in patients with PCOS had a negative influence on carbohydrate metabolism. HOMA-IR increased which suggests increased insulin resistance [28], [29].

2.4 Lack of influence of the COCs on carbohydrate metabolism in women with PCOS

Some medical studies have shown no effect of COCs on HOMA-IR [30]. Other studies suggest that only a change of one’s lifestyle and taking at the same time COCs containing drospirenone plus metoformin improve carbohydrate metabolism [25]. Some trials showed that COCs did not increase insulin resistance, neither did they deteriorate postprandial glucose [31]. Other trials showed that COCs do not have any influence on glucose as well as insulin levels and do not change HOMA-IR in women with higher levels of testosterone. However, in healthy women COCs increased the insulin level and HOMA-IR [32]. In some cases it was concluded that taking COCs does not have any influence on insulin resistance in women with PCOS [33]. A Cochrane review examined the effectiveness of hormonal contraceptives on glucose tolerance. It showed that they do not have any significant influence on carbohydrate metabolism in women without diabetes [34]. Current studies suggest that there are no significant changes in carbohydrate metabolism after a short period of using COCs in women with PCOS. In general population the COC therapy was not associated with an increased risk of T2DM [35]. From population studies, conducted on healthy premenopausal women, it was concluded that COCs do not have any negative influence on the glucose metabolism [36]. One review suggests that current data do not indicate any negative influence of COCs on glucose metabolism. However, there is still a need for high-quality long-term prospective studies [37].

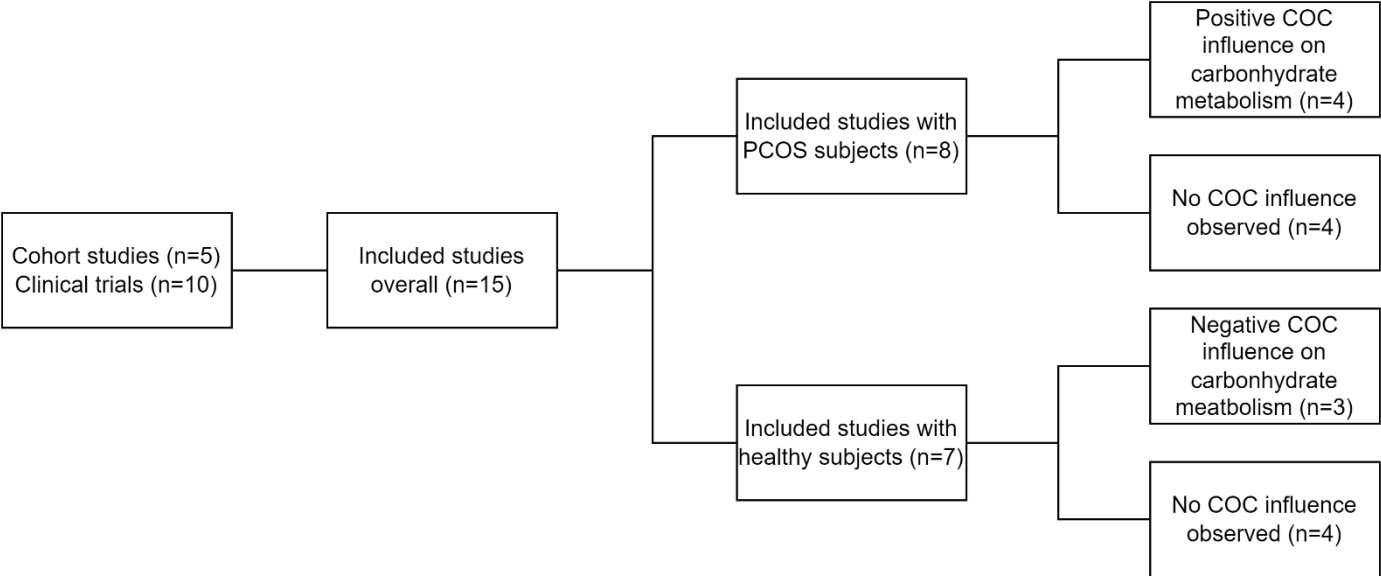


Figure 2. Types of studies and characteristics of the outcomes

Total number of subjects	Number of PCOS subjects treated with COCs	Number of subjects with PCOS	Age of healthy subjects	Age of PCOS subjects
10 094	672	830	18-50	14-48

Figure 3. Characteristics of pooled patients

Influence	Type of pills	Number of participants	Duration	PCOS
2. [21] NEGATIVE	Not specified	1879	<5 years N=89 >5years N=423	NO
3. [22] NEGATIVE	0.03 mg of Ethinylestradiol+ 0.075 mg of Gestodene N=4 N=17: 3 mg of Drospirenone + 0.03 mg of Ethinylestradiol N=17 30 mcg of Levonorgestrel N=9	55	At least 12 months	NO
6. [28] NEGATIVE	35 used COCs (not specified)	133	Not specified	YES
7. [26] POSITIVE	Group 1: 3 mg of DRSP/30 mcg of EE N=60 Group 2: 2 mg of CMA/30 mcg of EE N=60	120	6 months	YES
8. [27] POSITIVE	0.035 mg of Ethinylestradiol and 2 mg of Cyproterone acetate	70	6 months	YES
9. [25] POSITIVE	Group 1: 3 mg of DRSP plus 30 µg of EE/ N=32 Group 2: 2 mg of CPA plus 35 µg of EE N=36	99 (31 did not complete treatment)	6 months	YES
10. [24] POSITIVE	150 mg of Desogestrel + 30 mg Ethinylestradiol) N=30	of 90	12 months	YES

Figure 4. Characteristics of pooled studies

It can be noticed that androgen receptor agonists- levonorgestrel, norgestimate, gestodene-worsen carbohydrate metabolism parameters and androgen receptor antagonists- DRSP, CPA- may improve these parameters. In our study only desogestrel, despite acting as an androgen receptor agonist, showed the positive influence on carbohydrate metabolism parameters.

Authors/ Year of publication/ Time of study	Design	Number/age of patients	Target of study	PCOS YES/ NO	Type of pills	Duration of therapy	Outcomes (change in indicators of carbohydrate metabolism)
Marzena Malara et. al [17] 2020/ not reported	Cohort	N=123 Not reported	To compare the indicators of carbohydrate metabolism between women with a 2/3-year history of COCs use and non-users within last 3 years	NO	All women take fourth generation of COCs containing thinlyestradiol (0.02-0.03 mg), but with different progestins (3 mg of drospirenone or 0.15 mg of desogestrel, or 0.15 mg of levonorgestrel)	2-3 years	No difference in a fasting glucose level and a fasting insulin level between the groups
Annina Haverinen et. al [16] 2020 2015-2018	Randomized, open label, controlled, clinical trial	N=77 18-35	To compare the influence of different type of COCs on insulin sensitivity by determining the indicators of carbohydrate metabolism	NO	Group 1: EV+DNG (1-2 mg/2-3 mg) N=20 Group 2: EE+DNG (0.03 mg/2 mg) N=19 Group 3: DNG-only (2 mg) N=17	9 weeks	Insulin level did not change in any group. Mean fasting glucose level remained stable at the end of study. The difference between the groups in the fasting insulin level, HOMA-IR, ISI0 was not significant.
Santiago Palacios et. al [18] 2021 2012-2014	Prospective, double-blind, double dummy, randomized controlled trial	N=1190 18-45	A comparison of the influence on metabolic changes between COC use of 0.075 of desogestrel and COC use of 4mg of drospirenone	NO	DRSP (4 mg) (N=858) DSG (0.075 mg) (N=332)	5 cycles	No clinically relevant changes were observed in the mean or median values of insulin, plasma fasting glucose levels and C-peptide.
Christine Klipping et. al [19] 2021 2016-2017	Single-center, randomized, open label,	N=99 18-50		NO	Group 1: 15 mg of E4 /3 mg of DRSP (E4/DRSP) (N = 38)	6 cycles	Fasting insulin and glucose levels, C-peptide and



	controlled, 3-arm, parallel				Group 2: 30 µg of ethinylestradiol (EE) /150 µg of levonorgestrel (LNG) (N = 29) Group 3: 20 µg of EE/3 mg of DRSP (N = 31)		HbA1c remained relatively stable in all treatment groups. Insulin resistance, calculated using HOMA-IR, increased after all treatments with no remarkable treatment differences.
M.E Mosorin et. al [21] 2020 2012-2014	Prospective longitudinal population-based cohort	N=1879 46 y.o	The effects of combined hormonal contraceptives, progestin-only contraceptives and nonhormonal contraceptives on the occurrence of preDM and T2DM in perimenopausal women	NO	A current use of combined hormonal contraceptives (type not strictly specified) N=153  current progestin-only contraceptives N=842  nonhormonal contraceptives N=884	<5 years N=89 and combined hormonal contraceptive users represent 32 of them  >5years N=423 and combined hormonal contraceptive users represent 111 of them	Current combined hormonal contraceptive users exhibited higher AUC glucose and lower Matsuda Index values compared to different groups.
N.N Osman et. al[22] 2020	Cohort	N= 55 20-40	To evaluate the effect of COCs on metabolic profile	NO	From 30 COC users N=4 : 0.03 mg of ethinylestradiol and 0.075 mg of gestodene N=17: 3 mg of drospirenone and 0.03 mg of ethinylestradiol N=9 30 mcg of levonorgestrel	At least 12 months of the COC use	There was a significant increase in serum glucose in the COC users compared to the control group.
Qin Wang et. al[20] 2016 1997 and 2001	Cohort	N=5841 24-49	To compare the influence of COC	NO	1.Non-users N=4149 2.COC users N= 1157	Not reported	No significant differences in fasting glucose

			users, progestin-only contraceptive users and nonhormonal contraceptive users on women molecular profile		The vast majority of women who were using COCs with either 20 mcg or 30–40 mcg of ethinylestradiol 3. Progestin-only contraceptive users N=535		levels between the groups but COC use was associated with increased serum insulin concentration.
Mina Amiri et. al[33] 2020 2016-2018	This study is a crossover randomized controlled trial	N=88 18-45	Do combined oral contraceptives (COCs) containing progestins with low androgenic or anti-androgenic activities have different effects on clinical, androgenic and metabolic manifestations of polycystic ovary syndrome (PCOS) to those containing levonorgestrel (LNG)?	YES	Group 1: First treatment : 30 µg of ethinylestradiol (EE) + 0.15 mg of LNG Second treatment: 30 µg of EE + 150 µg of DSG  Group 2: First treatment : 30 µg of EE + 0.15 mg of LNG Second treatment : 35 µg of EE + 2 mg of CPA Group 3: First treatment : 30 µg of EE + 0.15 mg of LNG Second treatment : 30 µg of EE + 3 mg of DRSP Group 4: First treatment: 30 µg of EE + 150 µg of DSG Second treatment: 30 µg of EE + 0.15 mg of LNG Group 5: First treatment :	6 months	No significant differences were detected between study groups at baselines for secondary outcomes including fasting glucose, fasting insulin levels and HOMA-IR.  Significant period effects have been observed for some of the outcomes including, fasting glucose, fasting insulin levels and at the end of 6 months of treatment, indicating that these outcomes significantly changed in the second half of treatment, compared to the first half, regardless of type of treatment.

					35 µg of EE + 2 mg of CPA Second treatment: 30 µg of EE + 0.15 mg of LNG Group 6: First treatment : 30 µg of EE + 3 mg of DRSP Second treatment: 30 µg of EE + 0.15 mg of LNG		
A. Podfigurna et. al[26] 2020	Clinical trial	N=120 Mean 27	To compare clinical, metabolic and hormonal parameters in women with PCOS following treatment with different combined oral contracepti ves- COCs	YES	Group 1: N=60 3 mg of DRSP/30 mcg of EE N=60 Group 2: 2 mg of CMA/30 mcg of EE	6 months	. After 6 months of CMA treatment the average serum fasting GLU level had significantly increased. There was no statistical difference in GLU level between treatment with DRSP and CMA for 6 months in women with PCOS. After 6 months of DRSP and CMA treatment, the average serum INS levels decreased significantly. HOMA-IR after 6 months of treatment had decreased. significantly in both group. No statistically

							significant differences were observed in INS level and HOMA-IR between the groups after 6 months.
M. N Kalem [27] 2016 2011-2012	Prospective clinical trial	N=70 Mean 19	To investigate whether there is any effect of combined oral contraceptive (COC) use on serum 25-hydroxy vitamin D [25(OH)D] levels in patients with polycystic ovary syndrome (PCOS)	YES	Pills containing 0.035 mg of ethinylestradiol and 2 mg of cyproterone acetate	6 months	HOMA-IR decreased significantly after treatment.
Qiu-Yi Wang et al [25] 2016 2011-2013	Prospective randomized clinical trial	N=99 <40 y.o	To compare the different effects of drospirenone (DRSP)-COCs with cyproterone acetate (CPA)-COCs, combined with metformin and lifestyle modifications in women with PCOS and metabolic disorders	YES	Group 1: 3 mg of DRSP plus 30 µg of EE/ N=32 Group 2: 2 mg of CPA plus 35 µg of EE N=36	6 months	Fasting glucose, AUC of glucose, and fasting insulin levels decreased significantly only in the DRSP group. AUC insulin significantly decreased after treatment in the CPA group. HOMA-IR significantly decreased in the DRSP group but not in the CPA group.
D.Glintborg et al. [24] 2017	Randomized, controlled clinical trial	N=90 18-39	To determine the possible effects of treatment with combined	YES	Patients were assigned randomly to 3 groups: 1 group: metformin (1 + 1 g/day), N=30	12 months	Treatment with metformin/ metformin + COCs was followed by decreased weight,

			oral contraceptives (COCs) and/or metformin on GLP-1 secretion and the risk of RH by measure changes in GLP-1, glucose, insulin and C-peptide during 5-h OGTT during COC treatment		2 group: COCs (150 mg of desogestrel + 30 mg of ethinylestradiol) N=30 3 group combined treatment: metformin + COCs N=30		insulin and C-peptide levels compared to COC-only treatment. The prevalence of reactive hypoglycemia during metformin + COCs treatment increased significantly and was unchanged during metformin and during COC treatment. Women with PCOS had significantly higher levels of insulin and C-peptide. Obese patients with PCOS had significantly higher levels of insulin, C-peptide and HOMA-IR compared to lean patients.
M. V De Diego [28] 2020	Retrospective, cohort	N= 133 14-48	To investigate the metabolic impact of currently used therapies in polycystic ovary syndrome	YES	Type of COCs used by subjects (N=35): sustained release vaginal ring with 11.7 mg of etonogestrel and 2.7 mg of ethinylestradiol; 2.5 mg of noregestrol acetate and 1.5 mg of estradiol; 3 mg of drospirenone and 0.02 mg of ethinylestradiol; 3 mg of	?	No significant difference in glucose, insulin levels, HbA1c, HOMA-IR were observed between the controls and COC users. In the inositol group there was a significant difference in the glucose level, HbA1c and HOMA-IR compared

					dienogest and 0.03 mg of ethinylestradiol; 100 mg of levonorgestrel and 0.02 mg of ethinylestradiol; being the preparation of 3 mg of drospirenone and 0.03 mg of ethinylestradiol		to no-treatment group.
S.Bodur et. al[29]	Randomized controlled study	N= 118 18-39	To evaluate the effects of 3 mg of drospirenone/30 µg of ethinylestradiol used alone or combined with 1700 mg of metformin on metabolic risk factors	YES	3 mg of DRSP/30 µg of EE	6 months	After six months of treatment serum fasting glucose levels did not demonstrate any significant changes in any of the groups.
S.M Bhattacharya et. al[31] 2016 2012-2014	Randomized trial	N=112 14-35	To compare the effects of 30 µg and of 20 µg of ethinyl estradiol (EE) among women with PCOS	YES	Group 1: COCs containing 30 µg of EE + 3 mg of drospirenone N=55 Group 2: COCs containing 20 µg of EE +3 mg of drospirenone N=55	12 months	There were no significant adverse effects on the studied biochemical variables (including PPG:PPI ratio) between the groups.

Figure 5. Overall characteristics of studies

### 3. Discussion:

#### 3.1 Limitations

The most relevant weaknesses in the resources used for this study are due to limitations in the research designs. There is a restricted number of longitudinal studies with long-term follow-ups. In some studies chosen for this review there is a small number of participants. Furthermore, the results of studies are presented by different measures which makes it difficult to compare the findings. We took under consideration all these things and decided to focus on describing the final result of each study.

Nevertheless, several limitations also apply to our review. The reason of it is mainly an exclusion of reports due to the document type or to their conditions.

## 3.2 Principal findings

### 3.2.1 Healthy women

In the majority of included studies a significant influence of oral contraceptives pills on carbohydrate metabolism in healthy women was not detected. Only in studies with long follow-ups some changes were observed. Firstly, women, that used COCs for longer than 6 months, had a significantly higher prevalence of diabetes and also they were diagnosed at a younger age. Similar outcomes were observed in another study in which the current duration of 5 years or more of combined oral contraceptive use was associated with an increased risk of T2DM compared with nonhormonal contraceptive use of the same duration. The use of COCs of less than 5 years was not associated with any glucose metabolism disorders. The use of COCs was not associated with preDM or T2DM when compared with the use of non-hormonal contraceptives. What is important is that two out of three of these studies are with long follow-ups and, simultaneously, only in these studies the influence of COCs on carbohydrate metabolism was detected. Outcomes from the third study with a 6-year follow-up are that there were only very small metabolic changes for the persistent users of COCs in comparison with these women who were persistent non-users. For those women, who started to use the COCs, there were pronounced metabolic changes across the entire molecular profile. The metabolic changes were also pronounced for the women who stopped using COCs.

### 3.2.2 Women with PCOS

Outcomes from reviews about the influence of the COCs on carbohydrate metabolism in women with PCOS are ambiguous. There is about a fifty-fifty proportion observed in positive/negative influence of the COCs. Combined oral contraceptives consist of estrogens and progestins. There are different types of compounds which correspond to each part of pill. Various progestins show different influence on the androgen receptor. Some of them can act as androgen receptor agonists (desogestrel, levonorgestrel, norgestimate, gestodene) and the other as androgen receptor antagonists (cyproterone acetate, chlormadinone acetate, dienogest, drospirenone) [38]. It is worth to mention that pills, which are considered to act as androgen receptor agonists, more often in our review caused negative influence on carbohydrate metabolism. In contrast to this, if pills contained a progesterone part, which acts like an androgen receptor antagonist, the influence on carbohydrate metabolism was positive. An exception to this appeared to be a desogestrel which, despite of acting as an androgen receptor agonist, caused improvement in carbohydrate metabolism in women with PCOS.

### 3.2.3 Comparison with previous studies

There are studies in which negative influences of the COCs on carbohydrate metabolism are proved. Nevertheless, many of these studies were conducted many years ago (e.g. “The metabolic impact of oral contraceptives”) [39]. COCs, when they were introduced in 1960s, contained different compounds and amounts of hormones. A primary dose of estrogens was much higher. Over the years a successive decrease in estrogen dose has occurred and nowadays modern pills contain 15–30 µg of EE. Also progestogens have been developed in order to minimize the androgenic effects [40]. The common reason of studies conducted nowadays is the lack of influence of the COCs on carbohydrate metabolism.

The review called “Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus” by L.M Lopez included 31 trials [34]. The results of this study show that combined hormonal contraceptives do not cause clinically important changes in carbohydrate metabolism in women without diabetes. In “Effects of oral contraceptives on

metabolic parameters in adult premenopausal women: a meta-analysis”, which included 82 clinical trials by L. S. Sliva-Bermudez [32], the outcomes were similar- COCs have minor or no effects on HOMA-IR and glycemia.

One of the studies, which included women with PCOS, was a meta-analysis that included 35 studies. The outcome was that there was no association between COC use and any change in carbohydrate metabolism (no fasting insulin, no fasting glucose, no HOMA-IR change) [41]. In another retrospective trial the effect of different type of COCs was compared. Women with PCOS using COCs containing drospirenone had a significant decrease in fasting glucose and insulin levels after 6 months compared to women using COCs containing desogestrel that increased both parameters [42]. However, further studies involving women with PCOS are necessary.

### 3.2.4 Conclusion

We performed a systemic review of studies to assess the metabolic effect of COCs on carbohydrate metabolism in healthy women and in women with PCOS. A significant impairment of carbohydrate metabolism in a short period of time was not detected in healthy women. In women with PCOS the results depended on the type of COCs used. Due to such limitations as a short follow-up period, a small amount of participants and a moderate quality of underlying studies, the results should be considered preliminary. Further studies with an adequate amount of participants and long follow-ups are essential to define the metabolic outcomes of COC therapy.

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