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THE USE OF COMBINED HORMONAL CONTRACEPTIVES AND OCCURRENCE OF METABOLIC SYNDROME: A NARRATIVE REVISION

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Abstract: Objective: The goal of this revision is to explain if the use of combined hormonal contraceptives (CHCs) can be correlated to metabolic alterations that may have an association on the occurrence of metabolic syndrome. **Methods:** Articles published between January 2008 and September 2020 identified in Google Scholar, Scielo, Pubmed, and Cochrane databases were enlisted and narrowed down to 28 selected articles and one Ph.D. thesis. **Results:** The use of CHCs may influence carbohydrate metabolism, lipid profile, and changes in C-reactive protein (CRP), however, the influence of CHCs on abdominal circumference, blood pressure, and the prevalence of metabolic syndrome is unclear. **Conclusions:** The results found were controversial in most of the investigated cases of metabolic alterations. Therefore, there is no association between the use of CHCs and the occurrence of metabolic syndrome.
Keywords: Metabolic syndrome, contraceptives, metabolism.

INTRODUCTION

Metabolic Syndrome (MS) is characterized as a set of clinical risk factors involving anthropometric and biochemical changes, which result in an increased risk of type 2 diabetes mellitus (DM2) and cardiovascular disease.[1] The pathophysiology of MS is complex and multifactorial, resulting from genetic and environmental interactions. Currently, the most common definitions are those provided by the National Cholesterol Education Program Expert Panel (NCEP), Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF).[2]

Diagnosis is established by common criteria in which at least three parameters are present: increased waist circumference; triglycerides ≥ 150 mg / dL or treatment for them; HDL <50 mg / dL in women or specific treatment; blood pressure ≥ 130/85 mmHg or specific treatment; and fasting glucose ≥ 100 mg / dL or known DM2.[2] MS has been implicated in the induction of an inflammatory process that can culminate in the occurrence of cardiovascular disease and ultrasensitive C-reactive protein (CRP) has been a well-studied marker to measure this risk.[1]

Combined hormonal contraceptives (CHCs), which emerged in the 1960s, currently represent the most widely used contraceptive method in the world.[3] It is estimated that over 80% of sexually active women in the United States use the birth control pill.[4] In its composition, an estrogen and a progesterone are present, with ethinylestradiol (EE) being the most common estrogen in most formulations.[3,5]

The main mechanism of action of HCCs is related to the inhibition of ovulation, however, some metabolic effects related to the metabolism of carbohydrates, liver proteins and clotting factors have been associated with their use.(6,7) The use of HCCs is also related to the risk of thromboembolic and cardiovascular events, however, they are still considered a safe and effective family planning option. Regardless, the risks and benefits involved in each case must be evaluated. [3,7,8]

The prevalence of MS has increased significantly in recent decades, ranging from 22 to 39%, and has been considered an epidemic disease, with a higher prevalence in women than in men.[1,6] This variation can be explained according to the definition used.

The goal of this narrative revision is to understand the correlations between the use of HCCs and metabolic changes that may influence the occurrence of metabolic syndrome.

METHODS

KIND OF STUDY: This is a narrative revision of the literature.

Study project: To carry out this revision, the following order was followed: definition of the guiding question and GOAL of the research; criteria for inclusion and exclusion of publications were established; research was carried out in the literature, analysis and categorization of studies; the presentation and discussion of the results were implemented.

Search strategy: An automatic search was performed in the following databases: Google Scholar, Scielo, Pubmed, Medline and Cochrane libraries. The following keywords, in different combinations, were used to identify relevant studies: "oral contraceptives" or "hormonal contraceptive" and "cardiovascular risk" or "metabolic syndrome".

Ethical implications: As this work only addresses data in the public domain, the approval of an institutional ethics board was not required. However, the guidelines and regulatory norms of resolution 466/2012 of the National Health Council were respected. To avoid the practice of plagiarism, the researchers gave due credit to the authors used in the study.

Inclusion criteria: Articles published between January 2008 and September 2020 that were registered in a spreadsheet, where they could be classified according to study design, GOAL and conclusion, were included. Articles that were not directly related to the subject or could not be made available for reading were discarded. Subsequently, a manual search was carried out in the main journals identified in the thematic area and a revision of the list of references of selected articles. A total of 28 articles and a doctoral thesis were selected for analysis.

RESULTS AND DISCUSSION

WEIGHT CHANGES

Some cross-sectional studies have correlated the use of HCCs with changes in body mass index (BMI) (Table 01). However, the sample of some of these studies was not expressive among users and non-users of HCCs, had a small number of participants or used large and non-homogeneous age groups. [6,9-12]

A retrospective analysis in a cohort study of 2,086 women aged between 18 and 55 years divided HCC users by the time of use and showed that users with less than five years of use had a lower BMI compared to users aged 5 and 10 years.(13) Another study including 2,225 women, 85% of whom were not HCC users, sought to correlate changes that demonstrate increased waist circumference and duration of use and found no correlation.[10]

A Cochrane revision, whose GOAL was to assess the possible association between HCC use and weight changes, concluded that the available evidence was insufficient to determine the effect of HCC on weight. [14] Furthermore, the types of administration routes (oral, transdermal or vaginal) did not affect the BMI..[15]

CARBOHYDRATE METABOLISM

CHCs seem to exert some degree of influence on the mechanisms that regulate blood glucose, even in non-obese users. [16-18] Estrogen-associated progestin seems to exert more influence on the increase of insulin resistance, being the oral route more influential than the non-oral route..[17] Progestin, when administered alone, does not appear to interfere with carbohydrate metabolism.[19]

A prospective randomized study including 54 women using oral, transdermal and vaginal hormonal contraceptives showed effects on glucose metabolism, however, regardless of the route of administration.[15] However, in addition to the small sample size, the study was based on an observation time of only nine weeks, which was not sufficient to support the conclusion of the study (Table 02).

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Fakhraddeen *et al.*, 2016.[6]	Cross-sectional study. N = 246 (123 users and 123 controls).	Assess the risk of metabolic syndrome in contraceptive users.	Users were significantly more obese than non-users (p <0,001).
Santa *et al.*, 2016.[9]	Longitudinal and randomized study. N = 71 (20-40 years old).	See whether the use of HCC increases cardiovascular risk in Ghanaian women.	Comparison of the studied groups showed that HCC users had significantly increased BMI (p <0,001).
Asare *et al.*, 2014.[11]	Randomized cross-sectional study. N = 71 (47 users and 24 controls).	Determining the pattern of lipid profiles and the risk of cardiovascular disease in HCC users in the Ghanaian community.	The association between the use of HCC, orally and injectable, with the increase in BMI was significantly different from the results of the control group (p = 0.003 and p = 0.008, respectively).
Gallo *et al.*, 2014.[14]	Literature revision (Cochrane). (49 articles met the inclusion criteria).	Assess the potential association between the use of HCC and weight changes.	The available evidence was insufficient to determine the effect of HCCs on weight changes. No relevant effect was observed.
Mohamad *et al.*, 2013.[12]	Cross-sectional study. N = 200 (100 users and 100 controls).	Evaluate the effect of HCCs on lipid profile, blood pressure and BMI in women of reproductive age.	Women using HCC had increased BMI (p = 0,0004).
Lee *et al.*, 2013.[10]	Cross-sectional study. N = 2,225 (301 users and 1,924 controls).	Evaluate the effects of HCCs on cardiovascular risk factors according to duration of use.	Long-term use of HCC was not associated with abnormal waist circumference (p = 0,159).
Piltonen *et al.*, 2012.[15]	Prospective and randomized study. N = 54 (18 oral use, 18 adhesive use and 18 vaginal use).	Evaluate the effect of HCC administration routes on androgen secretion, chronic inflammation, glucose tolerance and lipid profile.	BMI values did not change considering the different routes of administration (oral, transdermal and vaginal) (p = 0,637).
Hurwitz *et al.*, 2009.[13]	Retrospective analysis cohort study. N = 2,086 (1,309 users and 777 controls).	Evaluate the differences in subclinical cardiometabolic measures in relation to the use of HCC, considering the duration of treatment and comparing with women who never used HCC.	Users with more than 10 years of use did not differ from those with 5 to 10 years of use (p <0.56); however, they were less likely to be obese than the other groups (p < 0.02).

Table 01 - Articles published between January 2008 and September 2020 that assessed the relationship between the use of hormonal contraceptives and weight variation.

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Marala *et al.*, 2020.[24]	Cross-sectional study. (N = 123 (25 users and 98 controls).	Analyze blood cortisol and other biochemical variables in HCC users and non-users.	There were no differences in blood glucose between groups.
Dokras, 2016.[20]	Literature revision.	Discuss the impact of using CHCs in relation to androgenic effects, metabolic profile and cardiovascular risk in patients with polycystic ovary syndrome (PCOS).	The risk of DM2 does not increase in women using HCC. No significant changes in carbohydrate metabolism were observed with the use of HCC in women with PCOS..
Fakhraddeen *et al.*, 2016.[6]	Cross-sectional study. N = 246 (123 users and 123 controls).	Assess the risk of metabolic syndrome in contraceptive users.	45,5% of HCC users were at high or very high risk of developing diabetes compared to 4.9% of non-users (p <0,001).
Cortés *et al.*, 2014.[16]	Literature revision.	Discuss the main effects of CHCs on glycemic regulation.	Hormonal contraceptives exert some influence on the mechanisms that modulate blood glucose.
Lopez *et al.*, 2014.[22]	Cochrane Revision. (31 articles met the inclusion criteria).	Evaluate the effect of CHCs on carbohydrate metabolism in healthy women and the risk of diabetes due to overweight.	There are no major differences in carbohydrate metabolism in non-diabetic women using different CHCs. Few studies, which makes it difficult to draw a conclusion based on strong evidence.
Lee *et al.*, 2013.[10]	Cross-sectional study. N = 2,225 (301 users and 1,924 controls).	Evaluate the effects of HCCs on cardiovascular risk factors according to duration of use.	HCC use and duration of use were not associated with changes in fasting blood glucose (p = 0,505).
Sitruk-Ware *et al.*, 2013.[17]	Literature revision.	Discuss the effects of hormonal contraceptives in modifying markers such as lipoproteins, insulin response and clotting factors associated with cardiovascular disease.	Progestins are related to increased insulin resistance. Anti-androgenic progestins have minimal effect on carbohydrate metabolism. The non-oral route of administration does not seem to have the same effect as oral administration, the results were worse in the oral use group.
Gourdy *et al.*, 2012.[23]	Guide created by experts from the French Society of Endocrinology.	Discuss the use of HCCs in women with vascular or metabolic risk factors based on international guidelines published by WHO (2009), adapted to the US context.	The revision concludes that, after starting HCC administration, there is no increase in fasting blood glucose or there is only a slight increase depending on the study. Most studies showed no changes in fasting blood glucose.
Olatunji *et al.*, 2012.[19]	An experimental study in animals. (N = 50 animals divided into five groups).	Evaluate the glucose tolerance and lipid profile associated with the use of HCC in female rats and whether these manifestations were related to the dose of estrogen or progesterone.	When compared to controls, animals that used the combination of EE and norgestrel had impaired glucose tolerance ($p < 0.05$). Effects on glucose tolerance were dose dependent..
Piltonen *et al.*, 2012.[15]	Prospective and randomized study. N = 54 (18 oral use, 18 adhesive use and 18 vaginal use).	Evaluate the effect of HCC administration routes on androgen secretion, chronic inflammation, glucose tolerance and lipid profile.	CHCs have unfavorable effects on glucose metabolism, regardless of the route of administration (p <0,008).

Frempong *et al.*, 2008.[18]	Cross-sectional study. N = 104 (21 CHC users and 83 controls) .	To evaluate the effect of using HCC on insulin resistance, glucose and triglyceride intolerance in African American women.	Fasting glucose did not differ between groups (p = 0.27). Insulin resistance was higher in the group of users (p = 0.09). Among non-obese women, users were more resistant to insulin than non-users (p <0,01).
Özdemir *et al.*, 2008.[21]	Prospective and randomized study. N = 63 (women with PCOS).	To investigate the effects of treatment with medroxyprogesterone acetate (MPA) for 10 days a month or HCC on lipid and carbohydrate metabolism in women with polycystic ovary syndrome (SOP).	Treatment of PCOS patients with MPA (p = 0.52) or HCC (p = 0.54) did not influence carbohydrate metabolism.

Table 02 - Articles published between January 2008 and September 2020 that evaluated the relationship between the use of hormonal contraceptives and carbohydrate metabolism.

The use of HCC appears to increase the risk of developing diabetes mellitus.[20, 21] A comparative cross-sectional study of 246 women showed a significant 45.5% risk of developing diabetes compared to 4.9% among non-users.[6] However, the group of HCC users also had a higher prevalence of family history of diabetes, suggesting that other risk factors must be considered in the assessment. The time of use also did not show any correlation with the influence on fasting glucose.[10]

Studies that correlated the use of CHCs with carbohydrate metabolism mainly reported an influence on glucose metabolism; some of these studies adopted a cross-sectional design and included small samples or were literature revisions. Studies that did not report the influence of the use of HCCs on carbohydrate metabolism corresponded to large literature revisions, used randomized samples or used a large sample and cross-sectional design.[6,10,15-23]

A comparative cross-sectional study with 123 women (25 users and 98 controls) showed that there were no differences between groups in fasting blood glucose.[24] A revision conducted by Cochrane evaluated the effect of hormonal contraceptives on carbohydrate metabolism and showed no important differences in different hormonal combinations and routes of administration in women without diabetes.[22] However, the number of studies on the subject was considered sparse for these conclusions and therefore the use of CHCs appears to have a modest impact on carbohydrate metabolism.[23]

CHANGES IN TRIGLYCERIDES

Or the use of CHC can increase levels of triglycerides. Two more studies were of cross-sectional development, with statistical significance and showing relationships between the use of HCC and the increase of two levels of triglycerides (Table 03).[9,12,18,19,24-26]

An experimental study using various combinations of contraceptives and exclusive progestagen showed that the group that used HCC showed significantly higher levels of triglycerides than the controlled group, or that it was not the case with exclusive progestagen use..[26]

A retrospective cross-sectional cohort study including 1,297 young women with polycystic ovary syndrome (PCOS) who had never taken CHC showed that triglyceride levels did not differ between the control and

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Marala *et al.*, 2020. [24]	Transversal study. (N = 123 (25 users and 98 controls).	Analyze blood cortisol and other biochemical variables in HCC users and non-users.	HCC users show a significant increase in triglycerides in relation to non-users (p <0,001).
Khatun *et al.*, 2019. [28]	Cross-sectional study. N = 40 (20 using CHC for up to 5 years and 20 using CHC for more than 5 years).	Assess the relationship between prolonged use of HCC and serum lipid profile.	Triglyceride level does not vary significantly with the use of long-acting oral contraceptive pills (more than 5 years) (p = 0,1).
Sufa *et al.*, 2019.[25]	Cross-sectional study. N = 365 (CHC users).	Determine the prevalence of dyslipidemia and its predisposing factors in women using HCCs.	Users of HCC have a high rate of dyslipidemia (34.8%). The standard deviation of the mean triglyceride level 108 ± 3,45.
Santa *et al.*, 2016.[9]	Longitudinal and randomized study. N = 71 (20-40 years old).	See whether the use of HCC increases cardiovascular risk in Ghanaian women..	Comparison of the studied groups showed that HCC users had significantly increased triglycerides (p <0,001).
Mes-Krowinkel *et al.*, 2014.[27]	Cohort, cross-sectional and retrospective study. N = 1,297. All patients had PCOS and never used HCC.	Evaluate the influence of HCC on anthropometric, endocrine and metabolic parameters in patients with PCOS.	Triglyceride levels did not differ between non-HCC users and those who used it for short (less than a year) or long term (more than 10 years).
Mohamad *et al.*, 2013.[12]	Cross-sectional study. N = 200 (100 users and 100 controls).	Evaluate the effect of HCCs on lipid profile, blood pressure and BMI in women of reproductive age.	Users of HCC showed a significant increase in triglycerides compared to non-users (p = 0,0001).
Olatunji *et al.*, 2012.[19]	An experimental study in animals. (N = 50 animals divided into five groups).	Evaluate the glucose tolerance and lipid profile associated with the use of HCC in female rats and whether these manifestations were related to the dose of estrogen or progesterone.	Both groups, one using EE and norgestrel and one using EE and levonogestrel had higher triglyceride levels than those in the control group. The use of HCC, but not the use of progestin alone, resulted in increased triglyceride levels. This effect of triglycerides was not dose dependent. (p <0,05).
Haarala *et al.*, 2009. [26]	Cross-sectional study. N = 1,257 women (24-39 years old).	Identify whether the metabolism, lifestyle and genetic determinants of CRP differ between women who use HCC and those who do not use any hormonal contraceptives.	Median triglyceride values were significantly higher in HCC users than in non-users; however, they revealed a significant association only in women using high doses of progestin or cyproterone (p<0.001).
Frempong *et al.*, 2008.[18]	Cross-sectional study. N = 104 (21 CHC users and 83 controls).	To evaluate the effect of hormonal contraceptive use in relation to insulin resistance, glucose and triglyceride intolerance in African-American women.	Increased levels of triglycerides were observed in users (p <0,001).

Table 03 - Articles published between January 2008 and September 2020 that assess the relationship between the use of hormonal contraception and the alterations of two triglycerides.

experimental groups, including short-term use (less than one year) and long-term use (more than 10 years).[27] In another publication, too, triglycerides do not vary significantly with the long duration of HCC.[28]

CHANGES IN HDL CHOLESTEROL

The use of HCC was associated with worsening HDL levels in most publications.[6,9,10,12,15,18,19,24,25] This effect occurred regardless of the route of administration, being dose-dependent on estrogen and not related to the use of exclusive progestin.[15]

In other publications, however, there was no evidence of a significant effect on HDL levels (Table 04).[17,21,23,27] In patients with PCOS, HDL levels did not differ between users and non-users of HCCs.[27]

In a cross-sectional study to assess the relationship between long duration of HCC use and serum lipid profiles, total cholesterol and triglyceride levels did not significantly vary with long duration (more than 5 years) of oral contraceptive pill use.[28]

CHANGES IN BLOOD PRESSURE

EE, present in most HCCs, is associated with the production of angiotensinogen, which can influence the elevation of blood pressure through the renin-angiotensin-aldosterone system.[29] This phenomenon can occur even in the presence of low doses of this hormone and has no correlation with the route of HCC administration.[3]

Some studies reported increased blood pressure levels among users compared to the control group, with some considering age matching, however, sample sizes were relatively small for data analysis. Other studies, some of them with large samples, did not show a correlation between the use of HCC and increased blood pressure (Table 05).[3,6,9-12,30]

In a study with 2,225 women, of which 301 users of HCC, there was no evidence of change in blood pressure among users, even in those who used it for more than 12 months.[10] Another study, which also did not consider a correlation between HCC and systemic arterial hypertension (SAH), analyzed the corrected data considering ethnicity, as the prevalence of SAH is higher in some ethnic populations..[27]

CHANGES IN PCR

The increase in CRP has been associated with the use of HCC and directly related to the increase in triglyceride levels, regardless of the route of administration used..[15,26,31]

A cross-sectional study of 1,257 women between 24 and 49 years old assessed whether the metabolism, lifestyle and genetic determinants of CRP differed between women who used HCC and those who did not use hormonal contraceptives; this study detected higher median CRP values among users than non-users, mainly associated with high doses of progesterone. In addition, the study suggests that the use of HCC alters the metabolic determinants and gene regulation of CRP (Table 06).[26]

CRP levels may be subclinically increased in individuals with a predisposition to develop MS and are generally higher in women than in men with this syndrome..[32] In addition, CRP may increase independently of liver synthesis.[31]

Most studies correlated the use of HCC with a statistically significant increase in CRP.[15,26,31] In other publications, the correlation of increased CRP in contraceptive users was not considered.[20,33]

METABOLIC SYNDROME IN CONTRACEPTIVE USERS

The use of HCC does not significantly affect most parameters involved in the

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Marala *et al.*, 2020. [24]	Cross-sectional study. (N = 123 (25 users and 98 controls).	Analyze blood cortisol and other biochemical variables in HCC users and non-users.	HCC users showed a significant increase in HDL compared to non-users (p <0,040).
Khatun *et al.*, 2019. [28]	Cross-sectional study. N = 40 (20 using CHC for up to 5 years and 20 using CHC for more than 5 years).	Assess the relationship between prolonged use of HCC and serum lipid profile.	HDL level does not vary significantly with long-term (more than 5 years) HCC use. (p = 0,5)
Sufa *et al.*, 2019. [25]	Cross-sectional study. N = 365 (CHC users).	Determine the prevalence of dyslipidemia and its predisposing factors in women using HCCs.	Users of HCC have a high rate of dyslipidemia (34.8%). The standard deviation of the mean level of HDL 45.21 ± 7.7.
Fakhraddeen *et al.*, 2016. [6]	Cross-sectional study. N = 246 (123 users and 123 controls).	Assess the risk of metabolic syndrome in contraceptive users.	CHC users had lower HDL levels than non-users (p <0,001).
Santa *et al.*, 2016. [9]	Longitudinal and randomized study. N = 71 (20-40 years old).	See whether the use of HCC increases cardiovascular risk in Ghanaian women.	Comparison of the studied groups showed that HCC users had a significant increase in HDL (p = 0,09).
Mes-Krowinkel *et al.*, 2014. [27]	Cohort, cross-sectional and retrospective study. N = 1,297. All patients had PCOS and never used HCC.	Evaluate the influence of HCC on anthropometric, endocrine and metabolic parameters in patients with PCOS.	The lipid profile, including HDL, did not differ between users and non-users (p <0,05).
Lee *et al.*, 2013. [10]	Cross-sectional study. N = 2,225 (301 users and 1,924 controls).	Evaluate the effects of HCCs on cardiovascular risk factors according to duration of use.	The use of HCC was associated with worsening HDL levels (p = 0,038).
Mohamad *et al.*, 2013. [12]	Cross-sectional study. N = 200 (100 users and 100 controls).	Evaluate the effect of HCCs on lipid profile, blood pressure and BMI in women of reproductive age.	Total cholesterol (p = 0.0001), LDL-C (p = 0.002) and HDL-C (p = 0.833) increased in users.
Sitruk-Ware *et al.*, 2013. [17]	Literature revision.	Discuss the effects of hormonal contraceptives in modifying markers such as lipoproteins, insulin response and clotting factors associated with cardiovascular disease.	The estrogen component was correlated with a minimal influence on the lipid profile.
Piltonen *et al.*, 2012. [15]	Prospective and randomized study. N = 54 (18 oral use, 18 adhesive use and 18 vaginal use).	Evaluate the effect of HCC administration routes on androgen secretion, chronic inflammation, glucose tolerance and lipid profile.	HDL levels were increased in all routes of administration (oral, transdermal and vaginal) compared to controlss (p = 0,037, p <0,001, p = 0,002)
Gourdy *et al.*, 2012. [23]	Guide created by experts from the French Society of Endocrinology.	Discuss the use of hormonal contraceptive methods in women with vascular or metabolic risk factors based on international guidelines published by the WHO (2009), adapted to the US context.	The revision concludes that hormonal contraception has only a modest impact on lipid metabolism. Available data suggest that there is no excessive risk of using progestin-based contraceptives..

Olatunji *et al*., 2012.[19]	An experimental study in animals. (N = 50 animals divided into five groups).	Evaluate the glucose tolerance and lipid profile associated with the use of HCC in female rats and whether these manifestations were related to the dose of estrogen or progesterone.	Animals subjected to the use of the combination of EE and norgestrel showed worse HDL levels compared to controls. The use of HCC, but not the use of progestin alone, resulted in decreased HDL levels. The effects of HDL were dose-dependent. ($p < 0,05$).
Frempong *et al*., 2008.[18]	Cross-sectional study. N = 104 (21 CHC users and 83 controls).	To evaluate the effect of hormonal contraceptive use in relation to insulin resistance, glucose and triglyceride intolerance in African-American women.	Higher HDL levels were observed in female users ($p = 0.02$).
Özdemir *et al*., 2008.[21]	Prospective and randomized study. N = 63 (women with PCOS).	To investigate the effects of treatment with medroxyprogesterone acetate (MPA) for 10 days a month or HCC on lipid and carbohydrate metabolism in women with polycystic ovary syndrome (SOP).	Patients with PCOS using MPA did not show significant changes in lipids ($p = 0,080$).

Table 04 - Articles published between January 2008 and September 2020 that evaluated the relationship between the use of hormonal contraceptives and changes in HDL.

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Ribeiro *et al.*, 2018. [29]	integrative literature revision.	Identify evidence in the literature of the relationship between the use of different HCC and changes in blood pressure values in women.	There is evidence in the literature of blood pressure changes associated with different hormonal contraceptives and that personal history of morbidities must be considered in an attempt to reduce the effects on the cardiovascular system.
Fakhraddeen *et al.*, 2016.[6]	Cross-sectional study. N = 246 (123 users and 123 controls).	Assess the risk of metabolic syndrome in contraceptive users.	Hypertension was more prevalent in HCC users (p = 0,34).
Santa *et al.*, 2016.[9]	Longitudinal and randomized study. N = 71 (20-40 years old).	See whether the use of HCC increases cardiovascular risk in Ghanaian women.	Comparison of the studied groups showed that HCC users had a significant increase in blood pressure (p <0,001).
Asare *et al.*, 2014.[11]	Randomized cross-sectional study. N = 71 (47 users and 24 controls).	Determining the pattern of lipid profiles and the risk of cardiovascular disease in HCC users in the Ghanaian community.	Differences in elevated systolic blood pressure (BP) were not significant between groups, however, diastolic pressure was higher among users than non-users (p = 0,025).
Mes-Krowinkel *et al.*, 2014.[27]	Cohort, cross-sectional and retrospective study. N = 1,297. All patients had PCOS and never used HCC	Evaluate the influence of HCC on anthropometric, endocrine and metabolic parameters in patients with PCOS.	There were no significant differences in parameters between users and non-users (p <0,05).
Nisenbaum, 2014.[30]	Doctoral thesis. Prospective controlled study. N = 69 (36 CHC users and 33 controls).	Evaluation of heart rate variability, blood pressure and baroreflex sensitivity among users of 30 mcg EE and drospirenone compared to the control group.	There were no differences between users and non-users (p = 0,312).
Lee *et al.*, 2013.[10]	Cross-sectional study. N = 2,225 (301 users and 1,924 controls).	Evaluate the effects of HCCs on cardiovascular risk factors according to duration of use.	Long-term use of HCC was not associated with a change in blood pressure levels (p <0,2).
Mohamad *et al.*, 2013.[12]	Cross-sectional study. N = 200 (100 users and 100 controls).	Evaluate the effect of HCCs on lipid profile, blood pressure and BMI in women of reproductive age.	Users had increased systolic BP (p = 0.0007) and diastolic BP (p = 0.009).
Brito *et al.*, 2011.[3]	Literature Revision.	Assess the association between cardiovascular risk and use of hormone therapy.	EE exacerbated the production of hepatic angiotensinogen, which causes an increase in blood pressure by the renin-angiotensin-aldosterone system. EE alters pressure levels, even at low levels. There is no difference between the types of progesterone associated with EE in HCC

Table 05 - Articles published between January 2008 and September 2020 that assessed the relationship between the use of hormonal contraceptives and changes in blood pressure.

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Santos *et al.*, 2018. [33]	Cross-sectional study. N = 42 (21 users and 21 controls).	Test the hypothesis that there is a difference in plasma oxidized LDL values between women who use and do not use HCC, as well as evaluate the correlation between this and the lipid profile and hsCRP	A positive correlation was observed between oxidized LDL and LDL-cholesterol ($p < 0.05$), with total cholesterol ($p < 0.01$), with no correlation with us-CRP.
Dokras, 2016. [20]	**Literature revision.**	Discuss the impact of the use of CHCs in relation to androgenic effects, metabolic profile and cardiovascular risk in patients with polycystic ovary syndrome (PCOS).	CRP was related to adiposity in patients with PCOS; however, few studies have assessed the risk associated with the use of HCC.
Piltonen *et al.*, 2012. [15]	Prospective and randomized study. N = 54 (18 oral use, 18 adhesive use and 18 vaginal use).	Evaluate the effect of HCC administration routes on androgen secretion, chronic inflammation, glucose tolerance and lipid profile.	CRP was increased in all groups ($p < 0{,}002$).
Krintus *et al.*, 2010. [31]	Cross-sectional study. N = 128 (users between six months and three years duration), 94 non-users, 34 users, 14 (second generation) and 20 (third generation).	Evaluate the effects of second and third generation HCC on lipids, CRP and apolipoproteins.	CRP was significantly higher in third-generation HCC users. The main determinant of CRP in users were triglycerides ($p = 0{,}01$).
Haarala *et al.*, 2009. [26]	Cross-sectional study. N = 1,257 women (24-39 years old).	Identify whether the metabolism, lifestyle and genetic determinants of CRP differ between women who use HCC and those who do not use any hormonal contraceptives.	Mean values of CRP and triglycerides were significantly higher in HCC users than in non-users. However, they revealed a significant association only in women using high doses of progestin or cyproterone. PCR gene haplotypes were not significantly associated with PCR in both groups. $p < 0{,}001$.

Table 06 - Articles published between January 2008 and September 2020 that evaluated the relationship between the use of hormonal contraceptives and CRP alterations.

REFERENCE	KIND OF STUDY	GOAL	RESULT/CONCLUSION
Rauschert *et al.*, 2018.[35]	The subjects analyzed are from the 20-year follow-up of the Western Australian Pregnancy Cohort (Raine) Study.	Identify sex-specific differences in metabolism and their relationship to MS components in a young adult population.	The association of these metabolites differed between sexes with MS components, which means that the development of diseases such as obesity and diabetes can differ between sexes, potentially mediated by sex hormones..
Dokras, 2016.[20]	**Literature revision.**	Discuss the impact of using HCCs in relation to androgenic effects, metabolic profile and cardiovascular risk in patients with PCOS (SOP).	Patients with PCOS are at increased risk for MS. However, patients with risk factors for MS are not at increased risk with the use of HCC.
Fakhraddeen *et al.*, 2016.[6]	Cross-sectional study. N = 246 (123 users and 123 controls).	Assess the risk of metabolic syndrome in contraceptive users.	The prevalence of MS among users was significantly higher than among non-users (71.5% and 5.7%, respectively) (p <0,001).
Bentley-Lewis *et al.*, 2015.[5]	Literature Revision.	Discuss the diagnostic and therapeutic issues that physicians must consider when caring for women at risk for MS or when diagnosing MS.	Fatores de risco metabólicos podem estar presentes em usuárias de CHC, no entanto, não há evidências para apoiá-los como o fator causal.
Lee *et al.*, 2013.[10]	Cross-sectional study. N = 2,225 (301 users and 1,924 controls).	Evaluate the effects of HCCs on cardiovascular risk factors according to duration of use.	The estimated proportions of MS were 10.1% in non-users, 11.5% in short-term users (less than 12 months) and 16.1% in long-term users (more than 12 months), p = 0.89.
Verhaeghe, 2010.[34]	Narrative revision.	Discuss HCC options available to women with MS in Europe.	HCC did not appear to increase glucose intolerance in women with PCOS or a history of DM; furthermore, its effects on HDL cholesterol and triglycerides are comparable to those observed in women without MS.
Hurwitz *et al.*, 2009.[13]	Retrospective analysis cohort study. N = 2,086 (1,309 users and 777 controls).	Evaluate the differences in subclinical cardiometabolic measures in relation to the use of HCC, considering the duration of treatment and comparing with women who never used HCC.	Women using for more than 10 years and using up to 5-10 years had no increased risk of MS.

Table 07 - Articles published between January 2008 and September 2020 that assessed the relationship between the use of hormonal contraceptives and metabolic syndrome.

development of MS, even with prolonged use of the medication..[13,16]

A cross-sectional study with 2,225 women, including 301 HCC users, estimated the prevalence of MS to be 10.1% in non-users, 11.5% in users for less than 12 months and 16.1% in users for more than 12 months.[10]

Patients with PCOS are at increased risk for developing MS. However, in patients with clinical records of changes in weight, blood glucose or blood pressure, no significant impact of the use of HCC was reported for the development of MS.[20]

A comparative cross-sectional study with 246 women (123 HCC users and 123 controls) reports a significant prevalence of MS in HCC users represented in 71.5% of users and 5.7% of non-users.[6]

The use of HCC was not statistically significantly correlated with the presence of MS in most of the analyzed studies (Table 07).[5,10,13,33,34]

A cohort study identified sex-specific differences in metabolism and their relationship to the components of MS in a population of young adults. The association of these metabolites differed between sexes with MS components, which means that the development of diseases such as obesity and diabetes can differ between sexes, potentially mediated by sex hormones.[35]

CONCLUSION

The use of CHC can influence carbohydrate metabolism and increase triglyceride, HDL and CRP levels. The influence of HCCs on the parameters that determine waist circumference, blood pressure and the prevalence of MS is not clear. Therefore, there is no association between the use of HCCs and the occurrence of metabolic syndrome.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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