

REVIEW ARTICLE

C-Reactive Protein in Oral Contraceptive Users: Related Factors and Cardiovascular Risk

Alan Carlos Nery dos Santos¹, Jefferson Petto¹, Francisco Tiago Oliveira de Oliveira², Diego Passos Diogo¹, Ana Marice Teixeira Ladeia¹

Programa de Mestrado e Doutorado em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública – EBMS¹, Salvador, BA; Escola Bahiana de Medicina e Saúde Pública – EBMS², Salvador, BA – Brazil

Abstract

Studies show an association between the use of combined oral contraceptive (COC) and the elevation of C-reactive protein (CRP). However, it is unclear whether this increase represents cardiovascular risk, and what are the mechanisms involved in this association. Thus, our study aimed to review works that investigated the CRP levels in COC users, as well as describe the factors involved in this elevation. We considered eligible the studies indexed in EBSCO, EUROPUBMED, LILACS, PubMed and MEDLINE databases that evaluated the CRP of low-dose COC users, published between 2004 and 2015. The electronic search consisted of crossing the descriptors: Contraceptives, Oral, Combined; C-Reactive Protein and Inflammation, which resulted in 136 studies, of which 11 were eligible. They showed elevated CRP, even after ten days of use of COC. The most common CRP values were between 1-3 mg / L and > 3 mg / L, and in some studies values were greater than 10 mg / L. This indicates increased risk of future cardiovascular and metabolic events in this population. On the other hand, the main factors and mechanisms involved in the increase of this protein were hormonal, and, mainly, estrogenic and androgenic, and changes in function and levels of estrogen receptor β , high levels of cortisol and insulin resistance were documented. Other findings also indicate elevation of TNF- α , DNA hypomethylation in macrophages and alterations in the

hepatic production of CRP. Finally, the COC represents, as does obesity, 20% of the variation of CRP of women of reproductive age.

Introduction

Studies have indicated a link between the use of combined oral contraceptive (COC) with an increase in inflammatory parameters, especially of C-Reactive Protein (CRP) in healthy women of reproductive ages.¹⁻³ It has also been indicated that approximately one in every three women, users of COC, present CRP greater than 3 mg/L. Thus, aligned with other studies,^{1,4,5} this result may indicate high risks for cardiovascular and metabolic diseases in this population.

This thought is reinforced by studies that show that the CRP values present association with systemic arterial hypertension, dyslipidemia, coronary events, ischemic stroke, vascular and nonvascular mortality.^{1,6-8} Another interesting datum is the association between CRP and resistance to insulin and with certain markers of endothelial dysfunction, regardless of anthropometric measurements.⁹

Thus, by virtue of the gap regarding the risk of cardiovascular events and the mechanisms involved in the increase of CRP in COC users, our study aimed to review researches that investigated CRP in COC users, as well as describe the factors involved in this association.

Keywords

C-Reactive Protein; Women; Contraceptives, Oral, Combined; Risk Factors; Cardiovascular Diseases; Premenopause.

Methods

Study of systematic review to identify studies on COC effects over the plasma levels of CRP, as well as the risk of cardiovascular events and the factors related

Mailing Address: Alan Carlos Nery dos Santos

Escola Bahiana de Medicina e Saúde Pública. Av. Dom João VI, 275. Postal Code: 44657-086. Brotas – Salvador, BA – Brazil
E-mail: alansantos.pos@bahiana.edu.br

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to its increase. Therefore, articles related to other types of hormone-based contraceptives were not included. We considered eligible original studies with control group, published between 2004 and 2015, which evaluated women of reproductive age, > 18 years old, COC users for at least ten days, this being the shortest period related as capable to induce alterations to the CRP of this population.¹⁰

The following were not considered eligible: studies with animals, with menopausal women, with women affected by cardiovascular or metabolic diseases. Works that selected only obese, smokers, alcoholics, physically active women or under any medical treatment or food restriction were also excluded.

The searches to the databases selected in advance were made by independent revisers during the period from September to April 2016, wherein the search to the electronic database PUBMED/MEDLINE took place through the following crossover of terms Medical Subject Headings (MeSH): "Contraceptives, Oral, Combined"; "C-Reactive Protein"; "Inflammation", "Premenopause" and "Women".

For the LILACS/BIREME database, in the "words", "subject descriptors", "title words", "title" and "summary" fields, the following keywords were used as crossover descriptors: "Contraceptive Agents", "C-Reactive Protein", "Inflammation" AND "Premenopause". Finally, the searches to the EUROPUBMED e EBSCOhost bases followed the same selection standards, using the aforementioned keywords as crossings.

The screening process of the articles initially took place through reading the titles and summaries. Then, the articles that did not meet the selection criteria for this study were excluded. Thus, the articles that met the established criteria were recovered for reading of the full text, a new assessment regarding the eligibility criteria and extraction of the outcomes of interest of this review.

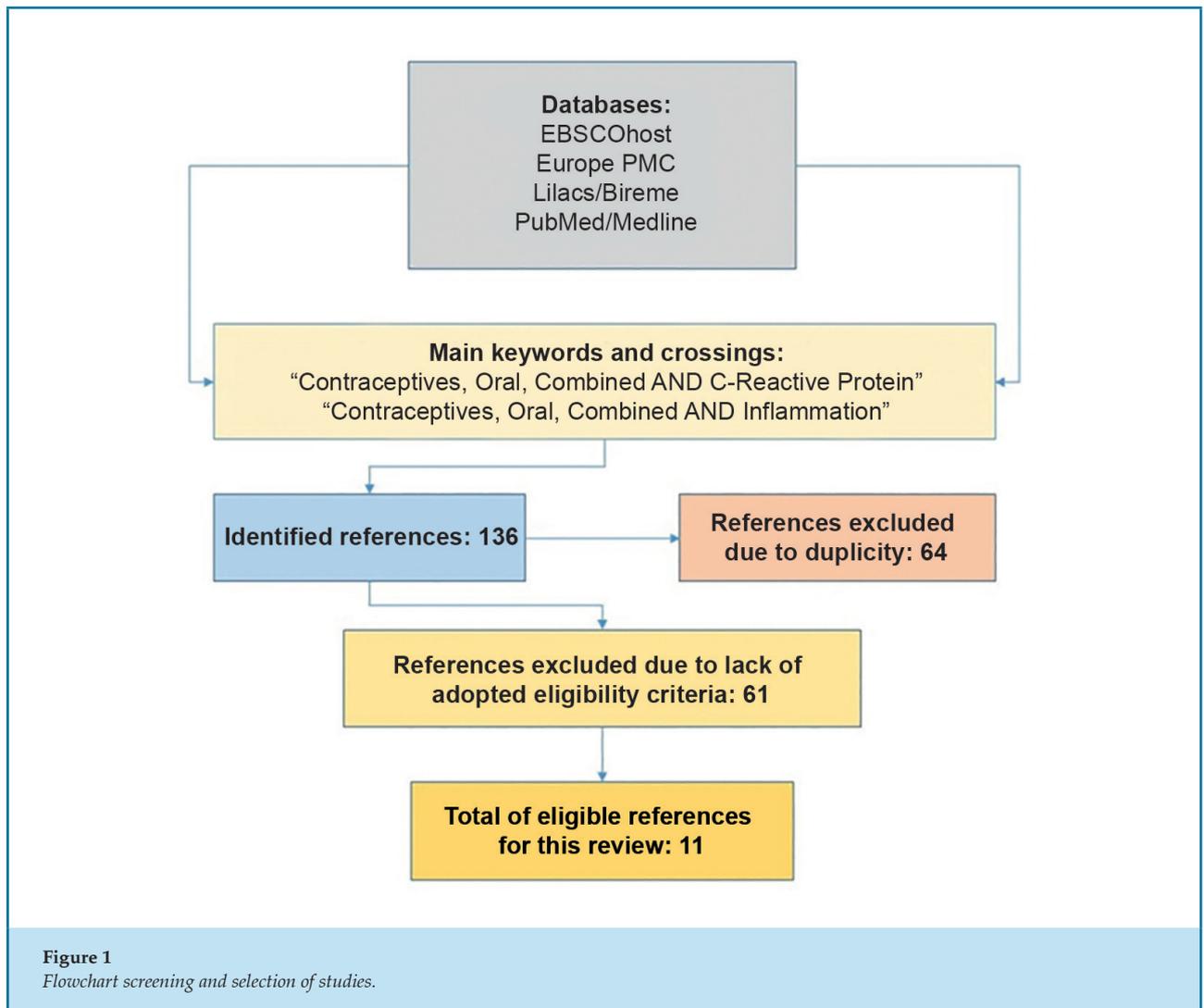
Following the pre-established methodological criteria, 136 references were identified, out of which only one was published in Portuguese. 64 references were excluded due to duplicity between the selected databases. Another 61 references were excluded for not fitting the established criteria or for not being related to the theme, where the main reasons for exclusion were: studies involving cardiovascular and metabolic risk groups, animal testing and women in menopause. Therefore, 11 studies were selected.^{1-3,8,10-16} Figure 1 sums the screening process and the selection of the studies that comprise this review.

Development

Although it does not have a perfect relation of cause and effect due to the observational methodology employed in most of the studies,^{1-3,8,13-16} an increase in CRP in women using COC has been suggested. It is interesting to note that a Finnish study comprised by 2,283 participants with ages from 24 to 39 years identified that 9 to 10% of the women in the research had CRP above 3 mg/L. Curiously, the prevalence was higher among women using COC, out of which 35% presented CRP > 3 mg/L. According to the authors, in young adults obesity is responsible for 20% of the increase of CRP, while in women, the use of COC is responsible for 20%, whereas, Dreon et al.¹⁵ identified COC as responsible for 32% in the increase of such protein.

Similarly, another interesting study with 822 young adult participants identified obesity as the main variable related with the increase of CRP in individuals from both sexes, in their 20s. However, once again the use of COC was the main responsible for the increase in CRP in adult women of reproductive age⁸. Corroborating these data, Buchbinder et al.¹⁶, with a sample of 850 blood donors, also identified obesity and COC as the independent variable for the increase of CRP in young adult women. In the occasion, the authors evidenced that the eutrophic women using COC presented CRP 3 times as high as obese women who did not use COC. It was also shown that the use of COC in obese women resulted in a CRP increase of 6 times in comparison with the non-obese.

Still in this aspect, studies^{3,13} with young women, without other possible factors that could induce the CRP increase, observed CRP twice as high values in the COC group. Another interesting point was the positive relation between CRP and the triglycerides, which may suggest an inflammatory profile with increased risk of cardiovascular diseases. However, Buchbinder et al.¹⁶ identified that lipid variables such as triglycerides, total cholesterol, low and high-density lipoprotein had smaller effects than COC in the increase of CRP in women, suggesting a high impact of the COC in the modification of CRP. The authors also suggested that the changes in CRP induced by COC were due to chronic ingestion of synthetic hormones, such as ethinyl estradiol and progesterone.



Although the relation between the current use of COC and the increase of the plasma values of CRP in women of reproductive age is still not clear, it is known that this event happens with second and third generation contraceptives.¹¹ Another intriguing point is that short periods (10 days) of treatment may provoke such modifications,¹⁰ and the longer the exposure time, the greater the chance of increasing CRP.¹²

It is interesting to note that 100% of the studies selected for this review showed higher values of CRP in women using COC when compared to women who do not use such drug.^{1-3,8,10-16} It is also stressed that the association between the use of COC and the increase of CRP remains significant even after adjustment into confounders, such as obesity.⁷ Although it has been suggested that values < 1, 1-3 and > 3 mg/L are, respectively, low, moderate and high risk indicators for future cardiovascular events,^{15,16}

Zieske et al.¹⁹ note that small elevations of this protein are associated to increase of risk of atherothrombosis during 20 years after the collection of the blood samples.

To this day, there are still gaps on the means through which COC use may induce the increase of CRP in women of reproductive ages, such as those comprising the selected articles. One of the possible mechanism seems to result from the direct action of COC in the hepatic synthesis of this protein.¹¹

Another factor would be the elevation of pro-inflammatory substances produced by the adipose tissue. Although van Rooijen et al.¹¹ point that the increase of CRP in COC users does not have any association with the increase in interleukin 6 (IL-6) and the Tumor Necrosis Factor – alpha (TNF- α), Divani et al.¹² observed a positive association between the values of CRP and those of TNF- α and IL-6 with the use of this drug.

The finding in question is reinforced in the study by Campesi et al.¹⁰, which pointed that COC users presented higher cortisol levels, a result that induces greater releases of the TNF- α . Still according to Divani et al.¹², the use of COC promotes hematologic and endothelial changes and hypomethylation to the total DNA of the monocytes. Such hypomethylation of the DNA is an important CRP increase mechanism, induced by functional alterations to the macrophages, which may occur regardless of the action of the androgenic hormones.¹⁰ According to Yudkin et al.⁹, modifications to the relation and activity of the α and β receptors of estrogen, represented by a lower expression of the β receptors in the monocytes-derived macrophages, provoke significant increase in the release of the TNF- α , which may be linked to higher plasma values of CRP.

Additionally, another possible strong mechanism promotor of the increase of CRP in women using COC is related to the insulin sensitivity. According to Beck²⁰, the progestins, synthetic hormones that mimic the effects of progesterone and are found in the COC, promote decrease in sensibility to insulin, a mechanism observed in a study performed by our group.²¹ The decrease of the sensibility to insulin triggers metabolic disorders that range from the increase of the fasting triglycerides to increased vascular inflammation.²² This alteration causes an increase in insulin production in an attempt to maintain glycaemia under appropriate levels and supply of glucose in the muscle cell. The increase in the circulating insulin levels causes a decrease in the activity

of the proteinaceous lipase and subsequent decrease in the uptake and utilization of triglycerides by the muscle tissue. This increases the amount of plasma triglycerides and, consequently, the circulating VLDL and LDL.^{22,23} As shown by O'Meara et al.²⁴, higher fasting triglycerides induce the increase in postprandial lipaemia. This mechanism explains why women using COC present higher fasting triglycerides and LDL and postprandial lipaemia than women who do not.²⁵ Both the increase in insulin and the elevation of the low and very low-density triglycerides and lipoproteins induce endothelial injury, a result that may induce the increase in CRP.

This hypothesis is reinforced by the findings of the study by Josse et al.²⁶, which did not observe differences in the HOMA index, one of the methods used to assess the insulin resistance, but found significant difference in HOMA Beta, which assesses the activity of the pancreatic beta cells among COC users and nonusers. That is, although they did not present high glycaemia or higher HOMA Index, the COC using women produce more insulin to maintain glycaemia in homeostasis due to lower insulin sensitivity.²⁶

However, despite the emphasis on hormonal and metabolic mechanisms in inducing the increase of CRP, we cannot ignore that the oxidative stress is another mechanism that may increase CRP in COC using women, as pointed by Dreon et al.¹⁵ Figure 2 presents the various mechanisms involved in increasing CRP by COC. It is worth to stress that our study is the first review on the theme.

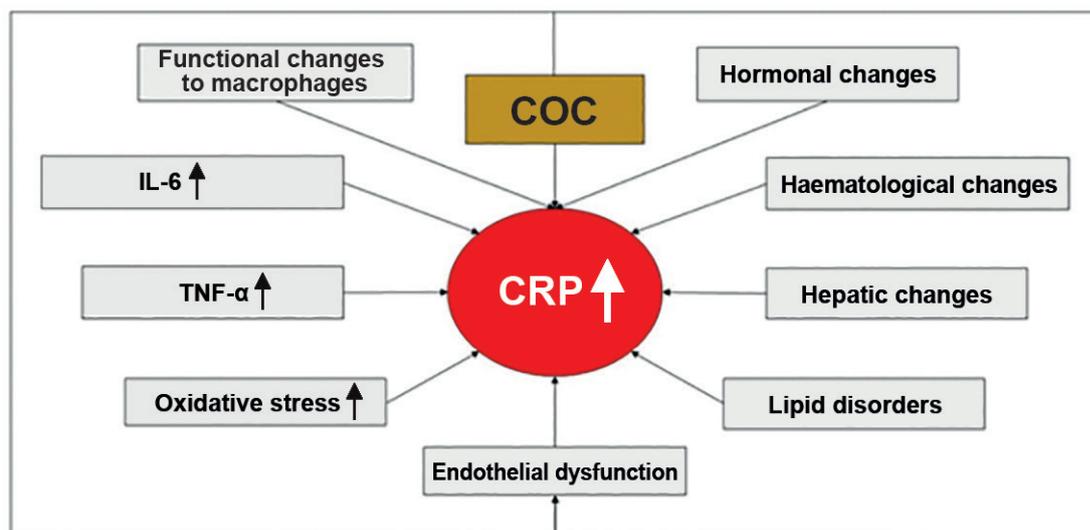


Figure 2

Factors involved in increase of CRP in COC users.

In sum, although the literature on the subject is scarce, the articles presented and discussed herein indicate that the use of COC causes an increase in CRP in women using COC, as well as support the hypothesis that this population is more subject to develop cardiovascular diseases and metabolic disorders^{3-5,13}. However, although the results point towards this direction, controlled clinical studies of longitudinal cut are still necessary in order to establish a relation of cause and effect and confirm such hypothesis.

Conclusion

Based on the analyzed studies, women of reproductive age that use COC, both short and long term, presented higher levels of CRP, which suggests a higher risk of cardiovascular events in this population. According to the studies, there are various factors that induce such increase, wherein the alterations in the hepatic synthesis of CRP, estrogenic and androgenic hormonal dysfunctions, decreased insulin sensitivity and the hypomethylation in the DNA of macrophages are possibly the main mechanisms that promote such increase.

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Author contributions

Conception and design of the research: Santos ACN, Petto J, Ladeia AMT. Acquisition of data: Santos ACN, Diogo DP. Analysis and interpretation of the data: Santos ACN, Petto J, Oliveira FTO, Diogo DP, Ladeia AMT. Writing of the manuscript: Santos ACN, Petto J, Oliveira FTO, Diogo DP, Ladeia AMT. Critical revision of the manuscript for intellectual content: Santos ACN, Petto J, Oliveira FTO, Diogo DP, Ladeia AMT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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