Original Article

# Potential association between oral contraceptives and oral diseases: A meta-analysis

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## Abstract

**Background:** Oral contraceptives (OCs) have been related to several systemic and oral diseases. Among oral diseases, the frequently encountered are periodontal diseases and alveolar osteitis.
**Objective:** The objective of the study was to assess the possible association between OC and oral diseases.
**Materials and Methods:** A PubMed search through 2018 considering the following medical subject headings terms "contraceptive agents" and "mouth diseases" was carried out. Studies with findings on OCs and mouth diseases were assessed. From 81 studies with full-text availability, 52 were excluded for several reasons: No clinical data (21), no usable/irrelevant data (26), and studies without a control group (5).
**Statistical Analysis:** RevMan 5.3 statistical program was used to analyze the results. The odds ratio (OR) with the Mantel-Haenszel method (dichotomous data) and the mean difference with the inverse variance method (continuous data), both with 95% confidence intervals were utilized.
**Results:** Main risk factors for osteitis alveolar were OC intake (OR: 2.32) and female gender (OR: 1.44). OC intake significantly influenced a greater bleeding on probing ($P < 0.01$) and a greater clinical attachment level loss ($P = 0.03$). On the contrary, it had no influence on other periodontal parameters such as plaque index, gingival index, or probing depth.
**Conclusions:** OC intake is closely linked to the risk of alveolar osteitis and, to a lesser extent, to periodontal disease risk.

## Introduction

The first oral contraceptives (OCs), introduced in the 1960s, had high concentrations of estrogen and progestin, which were related to increased risk of cardiovascular events. These important adverse effects led to the development of new drugs with progressively lower doses of estrogen and progestin. Modern formulations contain much lower doses and are associated with a much lower risk of cardiovascular events compared to the original formulations. In fact, at the present time, a healthy and non-smoker woman who takes OC does not have a greater risk of stroke than the rest of the female population, although they have a slightly higher risk of venous thromboembolism. On the other hand, OCs intake also has some beneficial effects such as a decreased risk of ovarian and endometrial cancer.[1]

OCs intake has been related to a higher incidence of periodontal diseases and of alveolar osteitis, the main post-operative complication of tooth extraction. The increase in plasma levels of steroid sex hormones that occur at puberty, pregnancy, or with OC intake has been associated with a higher prevalence and severity of both gingivitis and periodontitis. However, if modern OCs are considered, they do not have such a significant impact on periodontal tissues and should not be considered as a risk factor for gingivitis or periodontitis. [2] In the case of alveolar osteitis, despite numerous studies that analyze it, the findings are contradictory and do not show a clear association.[3,4] The objective of this study was to assess the possible effects of OC intake on oral tissues.

## Materials and Methods

Articles on OCs and oral diseases were searched in the PubMed database combining the medical subject headings terms: "Contraceptive agents" and "mouth diseases." A total of 196 articles (81 with full-text availability) from 1950 to 2016 were

found. The exclusion criteria were studies with no clinical data ($n$ = 21), studies with no usable/irrelevant data ($n$ = 26), and studies without a control group ($n$ = 5). Finally, the meta-analysis comprised 29 studies [Figure 1].

### Statistical analysis

The RevMan 5.3 statistical program (The Cochrane Collaboration, Oxford, UK) was used for meta-analysis. The odds ratio (OR) with the Mantel-Haenszel Chi-square formula (for dichotomous data) and the mean difference (MD) with the inverse of the variance method (for continuous data), both with 95% confidence intervals (95% CI) were applied. The Higgins statistic ($I^2$) established heterogeneity, using the random effects model when it was high. $P < 0.05$ was considered statistically significant.

## Results

Twenty-three studies[5-27] considered the prevalence of alveolar osteitis in women according to the intake or not of OCs [Figure 2]. Women who were taking OCs were 2.32 times more likely to develop an alveolar osteitis. Highly statistically significant differences were found (OR = 2.32, 95% CI: 1.96–2.74, $P < 0.001$).

Eighteen studies[5-7,9-11,13,15-21,23-25,27] examined the possible influence of gender on the prevalence of alveolar osteitis [Figure 3]. Women had a 1.44-fold higher the risk of alveolar osteitis compared with men, with a statistically very significant relationship (OR = 1.44, 95% CI: 1.13–1.84, $P < 0.01$).

Figure 4 shows the analysis of different periodontal parameters (plaque index [PI], gingival index [GI], and bleeding on probing [BOP]) regarding OC intake. Three studies[28-30] assessed the possible relationship between PI and OC [Figure 4a], although no statistically significant association was observed (MD = 0.02, 95% CI: −0.15–0.20, $P = 0.79$).

Another three studies[28,30,31] examined GI in women taking or not OCs [Figure 4b], without any statistically significant differences (MD = 1.00, 95% CI: −0.23–2, 22, $P = 0.11$). Two studies[28,29] analyzed BOP in relation to OCs [Figure 4c]. Women who took OCs had more BOP. After the statistical analysis, a very significant association was found (MD = 20.22, 95% CI: 7.44–33.00, $P < 0.01$).

Figure 5 presents the results of other periodontal parameters (probing depth [PD] and loss of clinical attachment level [CAL]) related to OCs intake. With respect to PD [Figure 5a], the five studies[28,29,31-33] that reviewed this parameter showed that OC intake did not affect PD, without a statistically significant

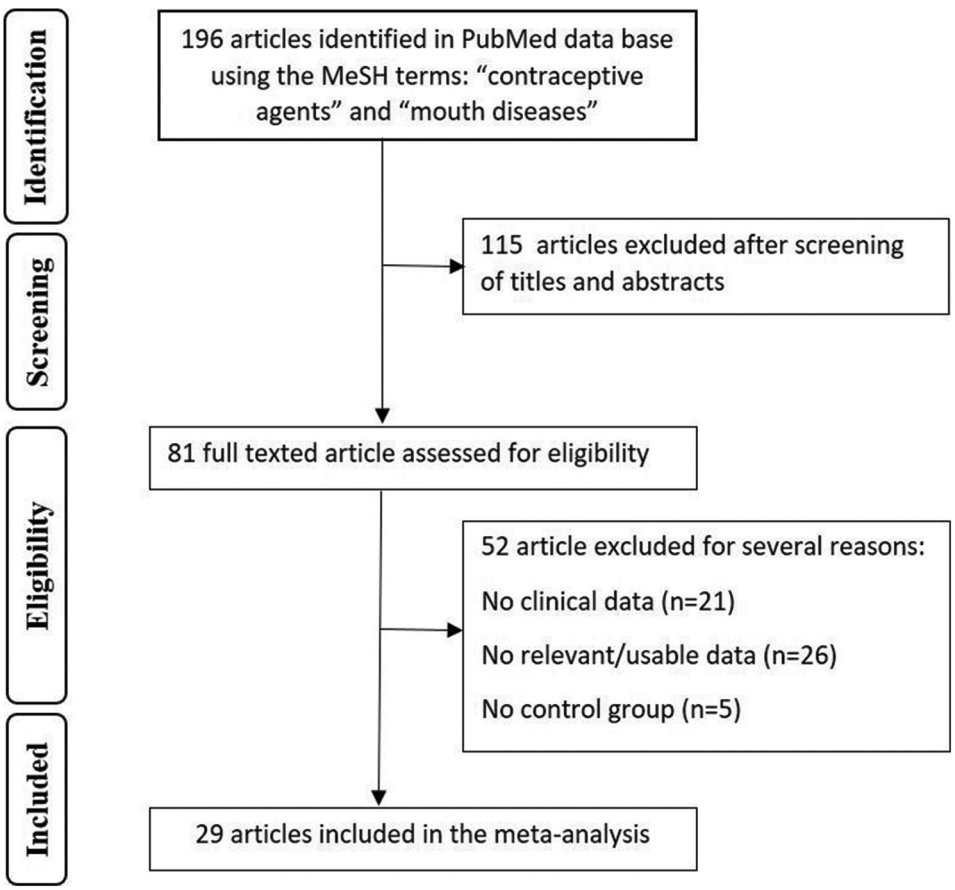


**Figure 1:** Study flow diagram

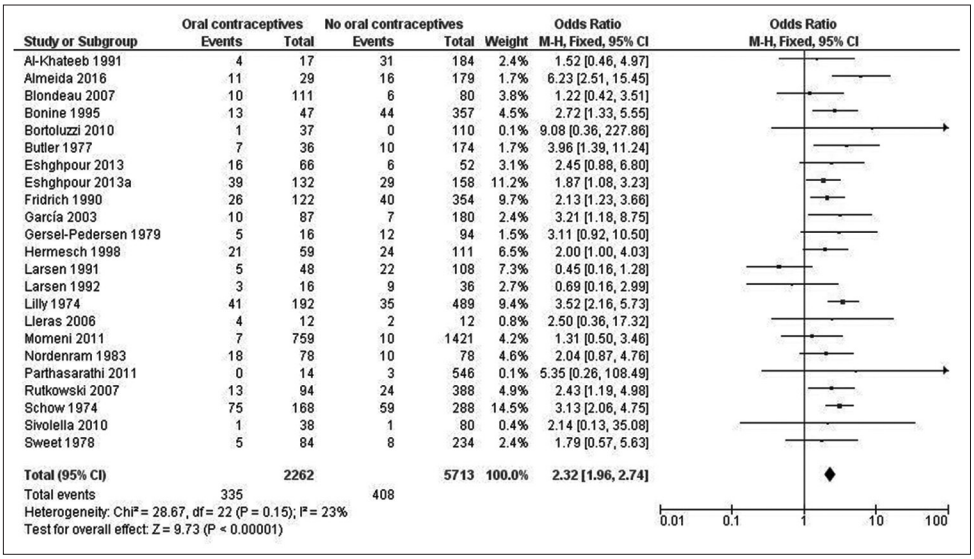


**Figure 2:** Study data and forest plot graph for the prevalence of alveolar osteitis in women with and without oral contraceptive intake

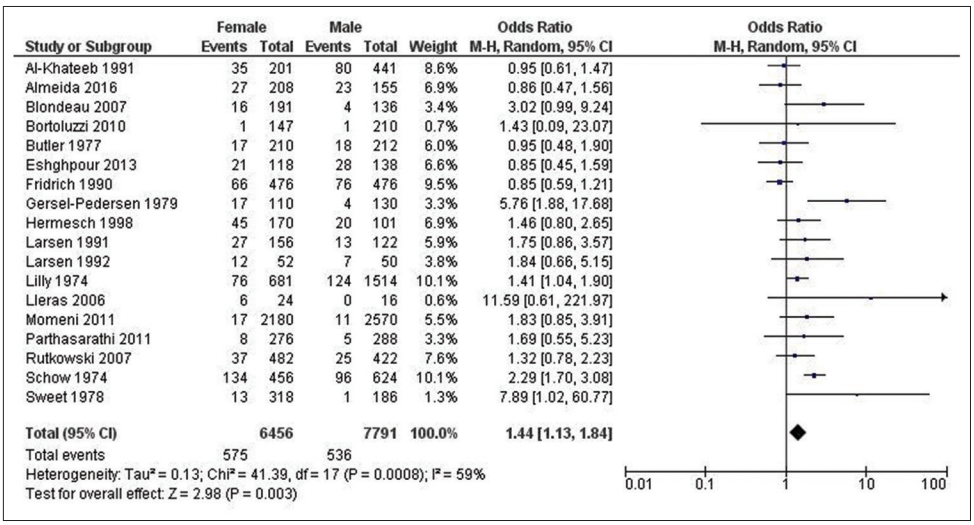


**Figure 3:** Study data and forest plot graph for the prevalence of alveolar osteitis according to gender

relationship (MD = 0.19; 95%: −0.03–0.40, $P$ = 0.08). Six studies[28-33] compared the loss of CAL in women who take OCs and those who do not take them [Figure 5b]. The loss of CAL was greater in women taking OCs, with statistically significant differences (MD = 0.16, 95% CI: 0.01–0.30, $P$ = 0.03).

## Discussion

In this meta-analysis on the possible effect of OCs intake on oral tissues, data from 29 studies have been included in the study. Several studies[5-16,19-27] note a higher prevalence of alveolar osteitis in women taking OC than in those who do not, suggesting a possible direct link between OC intake and alveolar osteitis. According to the present study, women taking OC were 2.32 times more likely to suffer from alveolar osteitis with a statistically significant association (OR = 2.32, 95% CI: 1.96– 2.74, $P$ < 0.001). One possible explanation is the increased fibrinolytic activity present in women taking OC due to an increase in estrogen concentrations that induce the dissolution of the clot and the possible development of alveolar osteitis.[12] However, two studies[17,18] did not observe a higher prevalence of osteitis alveolar among women taking OC. The results of these two studies[17,18] may be due to a lower age group of included cases and the relatively smaller sample size. In addition, a lower dosage of OC could also potentially explain the lack of any significant increase in alveolar osteitis.

In the present study, the possible influence of gender on the risk of alveolar osteitis was also analyzed. A higher prevalence of alveolar osteitis in females than in males was found, with a statistically significant relationship ($P$ < 0.01). Indeed, women

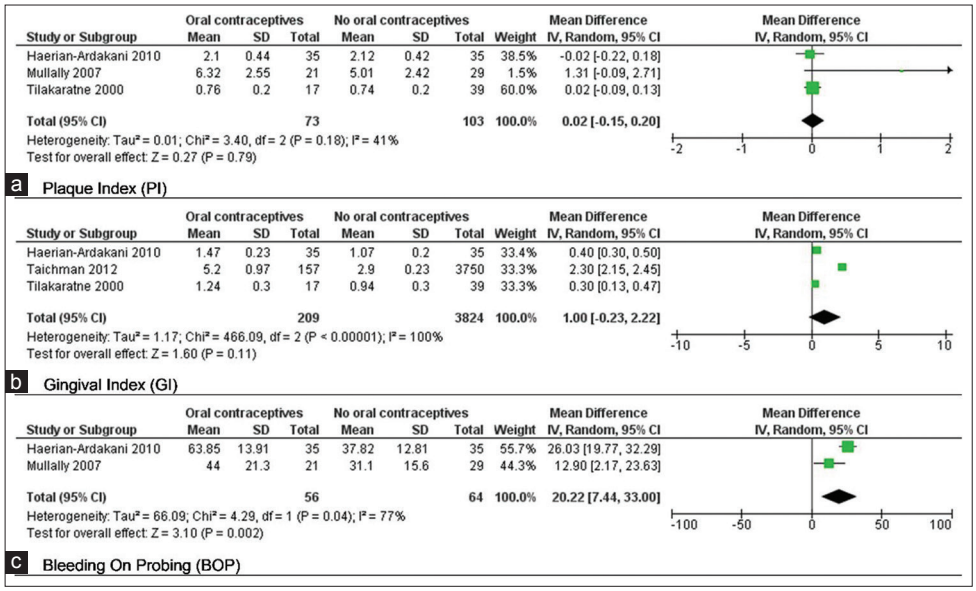


**Figure 4:** Study data and forest plot graph for plaque index (a), gingival index (b), and bleeding on probing (c) in women with and without oral contraceptive intake

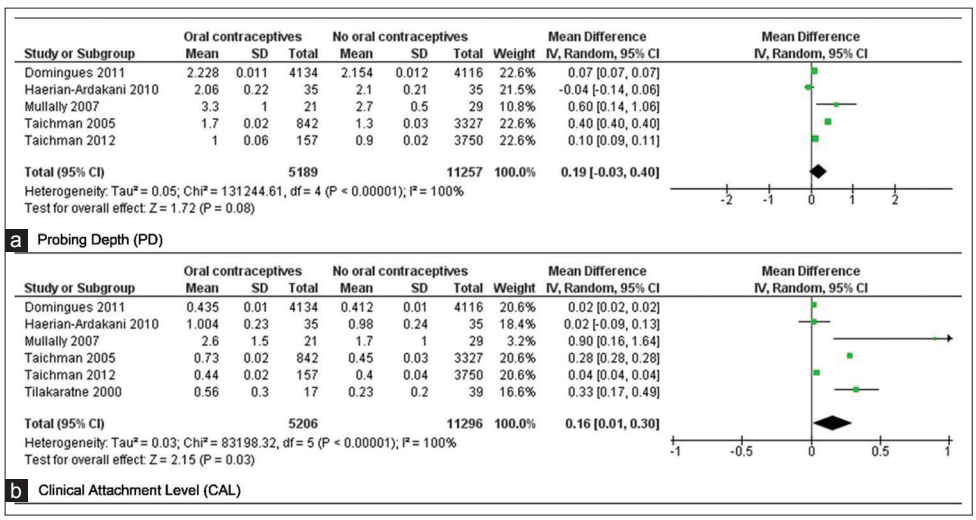


**Figure 5:** Study data and forest plot graph for probing depth (a) and clinical attachment level (b) in women with and without oral contraceptive intake

were 1.44 times more likely to suffer from alveolar osteitis. Thirteen studies[7,9,15-21,23-25,27] coincided in this predilection for the female gender; meanwhile, other five studies[5,6,10,11,13] did not find significant predilection for either gender. This higher prevalence of alveolar osteitis in women could be related to their OC intake.[27] The absence of gender-based differences could be due to the fact that the included studies did not consider the variations during the menstrual cycle and female hormone levels.[12]

The possible influence of OC intake with various periodontal parameters was also examined. Women taking OC did not show any statically significant increase ($P = 0.79$) in the dental PI. According to the results of the present study, GI also did not have a statistically significant association with OC intake ($P = 0.11$). The main factor that conditions gingival inflammation seems to be the concentration of steroid sex hormones, independently of the amount of dental plaque.[32] The current OCs have a very low concentration of these hormones with probably little influence on gingival inflammation.[2]

In this meta-analysis, women who took OCs had BOP significantly higher than that presented by women without OC intake, with a statistically significant association ($P < 0.01$). Two studies[28,29] coincided in indicating greater BOP in the women who took OC also with statistically significant differences. This

finding could be explained by the action of progesterone that promotes an increase in vascular permeability and facilitates the action of prostaglandins. The levels of prostaglandin E, one of the main inflammatory mediators, have shown to increase as steroid sex hormone levels increases. Analogously, these steroid sex hormones were capable of immune response disturbance by inhibiting both the chemotaxis of neutrophils and the phagocytosis.[28]

In the case of PD, no statistically significant relationship was observed ($P$ = 0.08) with OC intake. As previously mentioned, this may be due to the extremely low levels of progesterone and estrogens present in the current OCs, without a significant influence on periodontal tissues or on the risk of periodontal disease, especially in women with good oral hygiene habits.[32] However, the effects of OCs on periodontal tissues may be aggravated in women with a natural predisposition to periodontitis.[29]

Women with OC intake had a mean loss of CAL 0.16 mm higher than that of women who did not take them, with statistically significant differences ($P$ = 0.03). Again, the effects of steroid sex hormones on oral tissues should be contemplated, inducing an alteration in the microvascular tissue structure and its functions. There is an increase both in gingival crevicular fluid and permeability that together with vasodilation, exacerbates the inflammatory response, and could result in gingival hyperplasia.[32] Some studies indicate that this loss of CAL depends on the dose of OC and the intake time of the drug.[28,32]

The major limitation of the present meta-analysis is the heterogeneity of the included studies, especially with respect to the methodologies employed, the statistical analysis performed, and the variations in the sample size and characteristics.

## Conclusions

In this meta-analysis, risk factors for osteitis alveolar included OC intake (OR: 2.32) and female gender (OR: 1.44). OC intake significantly influenced a greater BOP ($P$ < 0.01) and a greater loss of CAL ($P$ = 0.03). On the contrary, it had no influence on other periodontal parameters such as PI, GI, or PD.

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