ADA CE Program ARTICLE 1

COVER STORY

Risk assessment and sensitivity meta-analysis of alveolar osteitis occurrence in oral contraceptive users

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ABSTRACT

Background. In this study, the authors conducted an alveolar osteitis (AO) risk assessment and global sensitivity meta-analysis within populations using oral contraceptives (OCs). Sex, smoking, and timing within the menstrual cycle were considered as factors.

Types of Studies Reviewed. Eligibility criteria for inclusion of a study in the meta-analysis were experimental or medical record survey data evaluating AO and OC use, ability to draw pairwise comparisons for factors of interest, and description of the number of AO events relative to the number of participants in the respective group.

Results. The risk ratio of AO in females not using OCs was 1.2 greater ($P \leq .05$) than that in males. Among females, OC use significantly increased ($P \leq .05$) the average risk of AO occurrence by nearly 2-fold (13.9% versus 7.5%). There was no statistical evidence of lower risk in females menstruating at the time of exodontia. In 85.7% of the studies, smokers had an overall higher rate ($P \leq .05$) of AO than did nonsmokers.

Conclusions and Practical Implications. To mitigate the increased risk of AO occurrence in females, the dentist should be cognizant of patients using OCs and smoking tobacco.

Key Words. ADA Foundation; women's health; tooth extraction; risk assessment.

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Alveolar osteitis (AO) is the most common postoperative complication in the healing of tooth extraction wounds.[1] This type of AO is known commonly as *alveolitis sicca dolorosa*, *localized osteitis*, or *dry socket*. Although the diagnostic criteria may vary, most authors characterize AO as a socket that is partially or totally devoid of a blood clot. This is accompanied by persistent severe pain, frequently requiring more than mild analgesia. Other symptoms may include halitosis and parageusia.

The causes of AO are not understood completely. A variety of risk factors (for example, anatomic, behavioral, pharmaceutical, and hormonal) have been described. Notwithstanding, for a single factor, these reports are sometimes contradictory. Particularly, the role of estrogen-related hormones play in AO occurrence is one area that continues to result in a variety of inferences. Our database search yielded review

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articles that summarized the literature associated with the etiology of AO and treatment regimens[1-7]; however, only 2 articles reported a quantitative assessment of published data.[8,9] In 1995, Cohen and Simecek[8] reported that under certain conditions females may have a 2- to 3-fold increase in AO risk compared with males. In 2015, investigators in a meta-analysis determined the risk ratio of oral contraceptive (OC) use on the incidence of AO in females with impacted mandibular third molars to be 1.8 greater than that of control participants.[9] Because OC users are reported to have notably higher risk, there is strong merit in analyzing other factors in this population.

Our objective was to conduct an AO risk factor assessment and global sensitivity meta-analysis within populations using OC. Specific aims included evaluation of the effect of OC use on sex-related effects, smoking tobacco use, and timing of exodontia in the menstrual cycle. We conducted a sensitivity analysis to rank these risk factors and interactions. Moreover, because prescribed doses of estrogen (for example, mestranol, ethinyl estradiol, estradiol valerate, or 17β-estradiol) in OC have continued to decrease over the past 20 years, we consider the incidence of AO over time in our analysis.

METHODS

Search strategy. We used MEDLINE at PubMed and the Cochrane Library as interfaces to identify literature. Using a Boolean search strategy, we searched for "oral contraceptive and dry socket OR birth control and dry socket OR oral contraceptive and alveolar osteitis OR birth control and alveolar osteitis OR oral contraceptive and alveolitis sicca dolorosa OR birth control and alveolitis sicca dolorosa OR oral contraceptive and localized osteitis OR birth control and localized osteitis" in all fields. We placed no restrictions on time frame, language, publication status, dental arch, or tooth type. We last conducted this database search on January 5, 2015. We identified additional resources by using reference lists of the obtained articles.

Selection criteria. We determined articles to be eligible for inclusion in the meta-analysis if the following criteria were met: original research article (experimental [prospective] or medical record survey [retrospective]) in which the investigators evaluated AO and OC use, ability to draw pairwise comparisons (treatment versus control) for factors of interest, and description of the number of AO events relative to the number of participants in the respective treatment group. For the latter, if the authors stated only the AO occurrence (percentage) and number of patients (or extractions), we performed simple calculations to estimate the number of AO cases.

Factors. Within populations using OCs, we considered sex, smoking, and timing of exodontia in the menstrual cycle as factors. For each factor, we dichotomized data and made pairwise comparisons. For sex, we made pairwise comparisons between males and females. To ensure that conclusions drawn about sex were not confounded by OC use, we also compared males with females not using OC. We dichotomized the analysis of OC use to users and nonusers. We dichotomized the timing of exodontia within the menstrual cycle to a time frame when menstruation did and did not occur. We dichotomized the analysis of smoking tobacco to smokers and nonsmokers.

One of us (D.R.B.) initially extracted data and subsequently corroborated the data by means of published reviews.[8,9] If we found differences, we reexamined the original publications to identify the cause for the discrepancy. We identified ambiguities and errors, jointly discussed them, and ultimately rectified them. Specifically, Larsen[10] reported the AO incidence in females not using OC as 9 of 36 tooth extractions. We excluded data from Gersel-Pedersen[11] because this author distinguished exudative alveolitis from alveolitis sicca dolorosa. We excluded data from Fridrich and Olsen[12] because they reported AO rates as percentages and left the total number of patients in each respective factor unspecified.

Synthesis of quantitative results. To conduct a comparative analysis of studies within each risk factor, we presented data graphically by using a forest plot following the manner of the Cochran-Mantel-Haenszel method. We used software (MedCalc for Windows, Version 15.8, MedCalc) to handle standard errors, 95% confidence limits, and adjustments for 0 (that is, in the numerator of the risk ratio) as described.[13,14] We calculated a pooled risk ratio with 95% confidence intervals and corresponding weights to determine whether there was a significant difference in the incidence of AO between the risk factor and its respective control group. We used the usual Q test and I^2 statistic to evaluate heterogeneity among studies.

Using main effects plots and analysis of variance, we conducted a sensitivity analysis to determine statistical differences and rank the various factors to determine which posed the greatest risk ratio ($risk_{treatment}$ / $risk_{control}$) via the Cochran-Mantel-Haenszel method, to estimate the various factor effects ($|risk_{treatment} - risk_{control}|$), and to compare and rank relative risk (|effect| / mean risk). We used this multipronged approach to ensure robustness of the ranking of risk factors.

We used a least squares linear regression to assess the potential drift of AO risk over time. We used statistical software (Dataplot, National Institute of Standards and Technology)[15,16] unless stated otherwise. For all analyses, $P \leq .05$ was considered significant.

RESULTS

Study selection. We identified 41 articles by using the described database search. Although we examined

ABBREVIATION KEY. **AO:** Alveolar osteitis. **AZT:** Azidothymidine. **F:** Female. **M:** Male. **OC:** Oral contraceptive.