Effect of Menstrual Cycle on Frequency of Alveolar Osteitis in Women Undergoing Surgical Removal of Mandibular Third Molar: A Single-Blind Randomized Clinical Trial

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Purpose: To measure the association between the menstrual cycle and the frequency of alveolar osteitis (AO).

Materials and Methods: In a study with a single-blind design, patients with bilateral impacted third molar teeth underwent randomized surgical extraction: one tooth during the menstrual period and one during the middle of the cycle. The postoperative examiner was unaware of the menstrual cycle status of the patients. The predictor variable was the timing of the menstrual cycle and was grouped as mid-cycle and menstrual period. The outcome variable was AO, which was measured (without knowledge of the menstrual cycle timing) at 2 to 7 days postoperatively. Other study variables included oral contraceptive (OC) use, smoking status, irrigation used during surgery, extraction difficulty, surgeon experience, number of local anesthetic cartridges used, and patient age. Appropriate bi- and multivariate statistics were computed, and the level of statistical significance was set at $P < .05$.

Results: A total of 145 female patients, with a mean age of 24 years, underwent 290 third molar extractions. The overall frequency of AO was 23.45%. The frequency of AO was significantly greater in the middle of the cycle than during the menstrual period inboth the OC users and nonusers ($P < .05$). Although OC users revealed a significantly greater frequency of AO compared with nonusers ($P < .05$), no statistically significant differences were found between the 2 groups during the menstrual period ($P > .05$).

Conclusions: According to the results of the present study, the menstrual cycle could be a determinant risk factor in the frequency of AO. We recommend that elective procedures be performed during the menstrual period in both OC users and nonusers to eliminate the effect of cycle-related hormonal changes on the development of AO.

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The most common complication after the extraction of permanent teeth is alveolar osteitis (AO).[1] According to previous reports, the frequency of AO in nonsurgical extractions has been 1-4% and 5-30% after surgical removal of mandibular third molars.[2] This complication develops 1 to 3 days after surgery, with severe and progressive pain, a foul taste, halitosis, and regional lymphadenitis.[3] Although AO is a self-limited phenomenon that will automatically resolve after 5 to 10 days, 45% of cases require up to 4 visits after extraction.[1]

The following risk factors have been reported for the development of AO: the experience of the

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surgeon,[4] the amount of trauma during surgery,[1,4] the difficulty of the surgery,[5] patient age,[1,6] smoking habits,[7,8] inappropriate irrigation during surgery,[9] preoperative infection,[10,11] use of local anesthetics,[8] and oral contraceptive (OC) use.[12,13]

Gender is also considered a determining factor in the frequency of AO. However, conflicting reports have been published regarding the role of gender. Sweet and Butler[9] found a frequency of AO in women that was 8 times greater than that in men, and Tjernberg[14] found a female-to-male ratio of AO frequency of 5 to 1. In contrast, Catellani,[15] al-Khateeb et al,[11] and Nusair and Younes[16] concluded that gender has no effect on the frequency of AO.

The purpose of the present study was to determine whether surgical removal of mandibular third molars in women during their menstrual periods differs from extractions during the mid-cycle regarding the frequency of AO. We hypothesized that the frequency of AO after surgical extraction of impacted mandibular third molars during menstruation would equal that at the mid-cycle; and that the frequency of AO after surgical removal of mandibular third molars in women using OCs would equal that of nonusers. The specific aims of the study were *1)* to measure the frequency of AO in OC users and nonusers after surgical removal of mandibular third molar teeth in the middle of the menstrual cycle and during the menstrual period, *2)* to compare the frequency of AO in the middle of the cycle versus during the menstrual period, and *3)* to compare the frequency of AO in OC users versus nonusers at the 2 points.

Materials and Methods

The present study was performed at the Mashhad Dental Clinic of Oral and Maxillofacial Surgery. All the patients provided detailed informed consent, and the Ethical Board of Mashhad University of Medical Sciences approved the study.

STUDY DESIGN

To address the research purpose, we designed and implemented a split-mouth, randomized, single-blind study in accordance with the consent statement and guidelines published in this issue.[17]

STUDY SAMPLE

The study population consisted of all female patients presenting for the evaluation and management of bilateral impacted mandibular third molar teeth from March 2010 to August 2012.

To be included in the present study, the patients had to be a woman, be 18 to 30 years old, have bilateral impacted third molars, and have a moderate difficulty level with their impacted teeth (on both sides), according to the sum of values regarding the spatial direction of the teeth, depth of impaction, and relationship with the ramus on the panoramic radiograph before surgery.[18]

The patients were excluded as study subjects if they were smokers, had systemic disorders, were lactating or pregnant, had received antibiotics during the previous 2 weeks, had any lesions found on the panoramic radiograph, or had received more than 2 anesthetic cartridges during surgery.

To prevent the different types of OCs confounding the findings, the OC users were asked to bring their pills before their surgical appointments. An expert checked the OCs, and the patients were excluded from the present study if they were taking progesterone-only pills; biphasic, triphasic, or quadriphasic pills; extended-cycle or continuous-cycle pills; or pills to relieve premenstrual dysphoric disorder symptoms. Hence, because the most common OCs used in Iran—according to the reports of the healthcare centers—are Low Dose (LD) pills (which consist of 0.03 mg ethinyl estradiol plus 0.15 mg levonorgestrel), according to the reports of the healthcare centers. Women who were taking monophasic-combination pills of LD to control pregnancy were included in the OC group.

STUDY VARIABLES

The predictor variable in the present study was the timing of the menstrual cycle. In each patient, the surgical extraction of one of the impacted mandibular molars was performed in the middle of the menstrual cycle and the contralateral molar was extracted during the menstrual period.

The outcome variable was the frequency of AO. Severe and progressive pain during the first week after surgery, along with a foul taste, halitosis, regional lymphadenitis, or loss of clot in the extraction socket, were the signs and symptoms resulting in a diagnosis of AO.

In addition, data were collected for the following variables: demographic variables, including age, medical variables, OC status and smoking status (current smoker vs nonsmoker). The preoperative variables included extraction difficulty (according to the radiographic findings) and surgeon experience. The perioperative variables included irrigation during surgery (volume of irrigation solution used) and number of local anesthetic cartridges.

DATA COLLECTION

All the procedures were performed by one experienced surgeon using the same protocol. Povidone iodine solution was applied around the mouth, and 2% lidocaine plus 1:80,000 epinephrine cartridges were used to block the inferior alveolar and long buccal nerves. Next, after a standard incision, a mucoperiosteal

envelope flap was created. If needed, bone removal, tooth sectioning, and bone recontouring were performed with a low-speed hand-held piece under sufficient sterile solution irrigation. The socket was irrigated with 60 mL of saline, and the flap was sutured using 3-0 silk sutures. A regimen of amoxicillin (500 mg, 3 times daily, n = 21) and Gelofen (400 mg capsules, 3 times daily, for a maximum of 3 days) was prescribed.

The participants were grouped into 2 categories according to their menstrual cycles. Based on the protocol explained to the patients, 1 of the impacted teeth was extracted during the few first days of the menstrual period (days 1 to 4 of the menstrual cycle), and the other impacted molar was extracted during the ovulation period (middle of the normal cycle). For the patients taking OCs, one procedure was performed in the middle of the pill cycle (days 10 to 13), and the other was performed during the interval between the two pill cycles—which was their menstrual period (days 24 to 27). Using this design, each patient served as her own control. Randomization of the surgery side in each category was performed using a coin flip.

Two follow-up appointments, 2 and 7 days after surgery, were held after each procedure to evaluate the healing process. In addition, the patients were asked to return if they experienced persistent or increasing pain from the second to fifth postoperative day. On these occasions, the patients were examined clinically for signs of AO. The follow-up examinations were performed by a calibrated examiner who had no information regarding the menstrual cycle timing of the procedures.

The cases of AO were treated with the following protocol: socket irrigation with normal saline; an intra-alveolar dressing with alvogyl iodoform (Septodont, Cambridge, ON, Canada); and a systemic analgesic prescription. In some cases, systemic antibiotics were also prescribed.

STATISTICAL ANALYSIS

Appropriate descriptive statistics (including the mean, frequency, range, and standard deviation) were computed for each variable. To analyze the data, binary logistic regression, χ^2, and t tests were performed, using the Statistical Package for Social Sciences software, version 11.5 (SPSS, Chicago, IL), with 95% confidence intervals.

Results

A total of 177 patients met the inclusion criteria. However, only 145 patients completed the study. Of the women who did not complete the study, 23 did not provide information regarding the status of their menstrual cycles or OC use and 9 had received the injection of more than 2 anesthetic cartridges. The mean age of the participants was 24.06 ± 5.21 years. Of the participants, 79 (54.48%) and 66 (45.52%) were OC nonusers and users, respectively. According to the t test results, the mean age of the women in the OC group (24.73 ± 5.98 years) was not significantly different statistically from that of the women in the non-OC group (23.34 ± 4.87 years; P = .561). The distribution of procedures at the 2 cycle points, according to the radiographic difficulty and numbers of cartridges, is listed in Table 1.

After the 290 procedures, 68 cases of AO occurred, for a frequency of 23.45%. According to the χ^2 test results, the frequency of AO showed no differences according to the various surgical difficulties, the number of anesthetic cartridges used, or age group. However, the frequency of AO had a significant association with the OC status of the patients (Table 2).

Using the χ^2 test, menstrual cycle timing revealed a significant association with AO frequency (Table 3). In addition, considering the logistic regression model, a significant difference in the frequency of AO was found when stratified by OC status and menstrual cycle timing (Table 4). Although the frequency of AO was significantly higher in the middle of the cycle in OC users compared with nonusers, no difference was found between the 2 groups during the menstrual period. Moreover, the frequency of AO was significantly higher in the middle of the cycle than during the menstrual period in both OC users and nonusers (Table 4).

The patients who returned with AO were treated according to the treatment protocol detailed in the

Table 1. STUDY VARIABLE DISTRIBUTION ACCORDING TO MENSTRUAL CYCLE TIMING

Variable	Menstruation	Mid-Cycle*	*P* Value
Sample size	145 (50)	145 (50)	—
OC users	66 (45.5)	66 (45.5)	1.000
Radiographic difficulty†			.854
5	66 (45.5)	65 (44.8)	
6	43 (29.6)	47 (32.4)	
7	36 (24.9)	33 (22.8)	
Cartridges used (n)	1.42 ± 0.49	1.36 ± 0.47	.229‡
Age (yr)	24.06 ± 5.21	24.06 ± 5.21	1.000‡

Data presented as numbers, with percentages in parentheses, or mean ± standard deviation.

Abbreviation: OC, oral contraceptive.

*Reference group.

†According to the sum score of the spatial direction of the teeth, depth of impaction, and relationship with the ramus on the panoramic radiograph.

‡Using a t test.

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Table 2. STUDY VARIABLE DISTRIBUTION ACCORDING TO AO FREQUENCY

Variable	AO		
	Yes	No*	*P* Value
Sample size (n)	68 (23.4)	222 (76.6)	—
Radiographic difficulty†			.819
5	32 (47.1)	99 (44.6)	
6	19 (27.9)	71 (31.9)	
7	17 (25.0)	52 (23.5)	
Cartridges used			.669
1	40 (58.8)	137 (61.7)	
2	28 (41.2)	85 (38.3)	
Age (yr)	23.67 ± 3.89	25.12 ± 6.32	.193‡
Age group			.719
18-24	43 (63.2)	135 (60.8)	
25-30	25 (36.8)	87 (39.2)	
OC use			.027
Yes	39 (57.4)	93 (41.9)	
No	29 (42.6)	129 (58.1)	

Data presented as numbers, with percentages in parentheses, or mean ± standard deviation.

Abbreviation: AO, alveolar osteitis; OC, oral contraceptive.

*Reference group.

†According to the sum score of the spatial direction of the teeth, depth of impaction, and relationship with the ramus values on the panoramic radiograph.

‡Using a *t* test.

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"Materials and Methods" section and were followed up until resolution of the AO.

Discussion

The purpose of the present study was to evaluate the effects of the menstrual cycle on the frequency of AO after the surgical removal of impacted mandibular third molars. Our first hypothesis was that the frequency of AO after surgical extraction of impacted third molars during menstruation would equal that at mid-cycle. The second was that the frequency of AO after extraction of impacted third molars in women taking OCs would equal that of nonusers. In addition, we aimed to measure and compare the frequency of AO in OC users and nonusers in the middle of the menstrual cycle and during the menstrual period. Both of our null hypotheses were rejected, because the frequency of AO was significantly higher among OC users and in the middle of the cycle compared with that in nonusers and during the menstrual period, respectively.

Table 3. FREQUENCY OF AO ACCORDING TO CYCLE TIMING

Menstrual Cycle Timing	AO (n)		Total (n)
	Yes	No	
Mid-cycle*	48	97	145
Menstruation*,†	20	125	145
Total	68	222	290

Abbreviation: AO, alveolar osteitis.

*Women who had teeth extracted mid-menstrual-cycle had a statistically significant increased risk of developing AO compared with during the menstrual period (unadjusted relative risk = 2.4; 95% confidence interval, 1.13-1.47; $P < .001$).

†Reference group.

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Table 4. ASSOCIATION BETWEEN MENSTRUAL CYCLE STATUS AND AO RISK ADJUSTED FOR OC STATUS

Variable	OR	95% CI	*P* Value
Intercept	2.777	1.74-4.41	<.001
Menstrual cycle*	3.159	1.75-5.71	<.001
OC status†	1.934	0.73-3.91	.022

Abbreviations: AO, alveolar osteitis; CI, confidence interval; OC, oral contraceptive; OR, odds ratio.

*After adjustment for OC exposure, the mid-cycle was significantly associated with a 3.159-fold increased risk of AO compared with the menstrual period.

†After adjustment for cycle timing, OC use was significantly associated with a 1.934-fold increased risk of AO compared with non-OC use.

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Moreover, we could not find any differences among the age groups, the various radiographic difficulties of the procedures, or the number of anesthetic cartridges used in the frequency of AO. According to the results of the present study, the frequency of AO was significantly higher in OC users than in nonusers in the middle of the menstrual cycle. However, no statistically significant difference was observed between OC users and nonusers during menstruation.

The most common complication after surgical removal of impacted third molars is AO. According to previous reports, the frequency of AO varies from 5% to 30%.[2] The results of the present study have shown that the frequency of AO after surgical extraction of impacted mandibular third molars was 23.45%, in accordance with that reported in previous studies.

The frequency of AO has increased since the introduction of OCs in the 1960s. Field et al[19] reported that the frequency of AO was insignificantly different between men and women in 1971; however, the difference was significant by 1983. They attributed this trend to the greater use of OCs in 1983, because

they had not excluded users in either survey. Schow,[20] Lilly et al,[21] and Garcia et al[22] reported that the frequency of AO in women using OCs was 2 to 3 times that of nonusers. The outcomes of the present study support the results of these reports, because we found that the total frequency of AO among OC-taking women was nearly double that of nonusers.

The higher frequency of AO relative to the use of OCs could be related to increased fibrinolytic activity during OC use. Hedlin and Monkhouse[23] observed that fibrinolytic activity increased 24 hours after the first administration of an OC. They also found great attenuation in fibrinolytic activity after the discontinuation of OCs. Catellani et al[12] found that women who had their third mandibular molar teeth extracted during days 1 to 22 of their OC pills had a higher frequency of AO than women undergoing extraction on days 23 to 28. The results of our study are in accordance with this earlier study; we observed a significantly higher frequency of AO in teeth extracted in the middle of the cycle (days 13 to 15) than in teeth extracted during the final days (days 25 to 27), when the women were no longer taking the OCs.

Menstruation occurs during the first 7 days of a normal menstrual cycle. During this period, the level of estrogen is at its lowest. During the next several days until ovulation, the estrogen level increases and reaches its peak concentration near ovulation.[24] Because estrogen has the potential to enhance fibrinolytic activity, the significantly higher frequency of AO in the middle of the cycle, compared with during menstruation, can be explained. In addition, the coincident estrogen surge with the external intake of estrogen through OCs could explain the higher frequency of AO in the OC group compared with the non-OC group, in the middle of their menstrual cycles.

Conflicting results have been seen regarding the role of gender in different studies. Sweet and Butler[9] and Tjernberg[14] found a frequency of AO in women that was 8 and 5 times greater than that in men, respectively. In contrast, Catellani,[15] al-Khateeb et al,[11] and Nusair and Younes[16] detected no difference between men and women regarding the frequency of AO. Because none of these studies reported the status of the menstrual cycle in their female patients, we believe that the probable reason for these conflicting findings was ignorance of the menstrual cycle.[5,9,11,14-16,25] No other controlled studies have addressed the role of the menstrual cycle in the frequency of AO in women not taking OCs.

The present study was a single-blind study; thus, the postoperative examiner had no knowledge of the cycle status of the patients. Because the study design was split-mouth, each patient served as her control. We also controlled for confounding factors in the frequency of AO, including surgical difficulty, surgeon experience, patient age, smoking status, irrigation, anesthetic cartridge number, and dosage of OCs.

Trauma could enhance the release of tissue activators, which could result in a higher frequency of AO.[10] Surgeon experience can also affect the amount of trauma that occurs during an extraction.[4,25] In addition, the surgical difficulty can determine the amount of trauma and, thus, the frequency of AO.[5] To eliminate these confounders, all the procedures were performed by one experienced surgeon, and all the procedures had the same difficulty level, according to the panoramic radiographic findings. We chose surgical extractions with a moderate difficulty level (sum score, 5 to 7), because it was the most prevalent type of impaction among the patients visiting the oral and maxillofacial clinic, according to the surgeon's experience (mostly mesioangular or horizontal, with a level B depth and class I or II ramus relationship).

The frequency of AO has been reported to be age dependent. The peak age has varied in the different reports. However, most studies have reported 20 to 40 years old as the peak age for the frequency of AO.[1,6,26] To overcome this risk factor and also because most elective procedures are performed in young patients at our oral and maxillofacial clinic, patient age of 18 to 30 years was one of the inclusion criteria applied in the present study.

Smoking is also a risk factor for the occurrence of AO.[7,8,25] It has been reported that smokers will have a significant reduction in the filling of extracted sockets with blood clots. The effects of smoking can be attributed to the suction and heat produced during smoking or to systemic mechanisms.[8] We excluded smokers to avoid the effect of study variations and to prevent bias.

Irrigation might be a risk factor for the development of AO.[9] Butler and Sweet[27] reported that irrigation with 175 mL of saline, rather than 25 mL, significantly reduced the frequency of AO. This benefit could derive from the removal of contaminants (debris, bacteria, and enzymes). In the present study, all the sockets were irrigated with 60 mL of saline, because it had an identical effect to that of high-volume lavage (170 to 350 mL).[28]

In addition, the possibility exists that epinephrine attenuates healing by reducing bleeding and oxygen tension and also by increasing fibrinolysis.[2] To eliminate this factor, procedures in which local anesthesia was administered by injection of more than 2 cartridges were excluded from the present study.

Catellani et al[12] reported that larger dosages of OCs increase the frequency of AO significantly. To eliminate factors relating to the type of OC, we limited the OC population to women who were using a single type of OC (monophasic, nonextended, noncontinuous, 21-day, combination pills).

Although we controlled for some confounding variables in the present study, other variables remained uncontrolled. The exact time of the hormonal surge during the menstrual cycle was one factor, the inaccuracy of which could have resulted in underestimation of AO frequency in the middle of the cycle. We also relied on the patients' estimations of their normal cycles, which was a possible source of bias.

In addition, a dilemma exists over the interaction between antibiotics and OCs. Oral antibiotic therapy could decrease the effectiveness of OCs and lead to pregnancy while taking OCs.[29] Although some case reports have supported this interaction, no pharmacokinetic and clinical data are available to establish this claim, except for data for rifampin.[29] In the present study, amoxicillin was prescribed for both OC users and nonusers. Considering the possible interaction between amoxicillin and OCs, the difference in the frequency of AO during the mid-cycle and menstrual period in OC users could have been masked and attenuated by this interaction. However, because the frequency of AO was significantly increased during the mid-cycle compared with during the menstrual period in OC users, this interaction had no confounding effect on the results of the present study.

In conclusion, within the limitations of the present study, the menstrual cycle had a prominent effect on the frequency of AO. Hence, we believe that the performance of elective surgery during the menstrual period could overcome the effects of the hormonal changes. Although taking OCs can dramatically increase the risk of developing AO, by scheduling the surgery on the days between tablet cycles, we could eliminate this risk factor. Additional studies are needed to investigate the effects of OC types, with precise determination of the hormonal levels.

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