Relationship Between Symptoms of Temporomandibular Disorders and Estrogen Levels in Women with Different Menstrual Status

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Aims: To evaluate whether serum estrogen level is associated with chronic pain, masticatory dysfunction, and depressive symptoms and/or somatization in women with temporomandibular disorders (TMD) and different menstrual cycle status. **Methods:** A total of 64 women were allocated into one of three groups: one composed of women with normal menstrual cycles (Group 1), one composed of pregnant women (Group 2), and one composed of women in surgical menopause (Group 3). All respondents underwent a standardized clinical examination with the Research Diagnostic Criteria for TMD (RDC/TMD). Diagnoses were generated according to Axis I, and grades of chronic pain, depressive symptoms, and somatization were evaluated according to Axis II. The level of serum estradiol was measured by using the immunofluorescent method. Analysis of variance, Kruskal-Wallis test with post hoc comparisons via series of Mann-Whitney *U* tests, and Spearman correlation coefficient were used for comparisons between study participants. **Results:** Reported pain was decreased with the progress of pregnancy among the women from Group 2 and was the lowest at the 36th week of pregnancy. Women in surgical menopause reported higher pain intensity as well as more difficulties with chewing and eating hard and soft food compared to the other subjects. Depressive symptoms and somatization were lowest among the women with advanced pregnancy and the highest among menopausal women. **Conclusion:** TMD-related chronic pain grade, masticatory dysfunction, and depressive symptoms and somatization are the highest when the estrogen level is the lowest. *J Oral Facial Pain Headache 2018;32:151–158. doi: 10.11607/ofph.1906*

Keywords: *chronic pain, estrogen, menstrual status, surgical menopause, temporomandibular disorders*

Temporomandibular disorders (TMD) encompass a set of clinical problems that involve the masticatory musculature and/or temporomandibular joints (TMJ).[1] These clinical conditions are the second-most prevalent cause of orofacial pain[2] and have a strong predilection for women, with a male to female ratio of 1:3.[3] The prevalence of TMD increases after puberty, reaches its highest peak in women of 20 to 40 years of age, and significantly decreases after menopause.[4] These epidemiologic data have sparked many different studies on links between TMD pathogenesis and female reproductive hormone levels, particularly estrogen.[4–7] Previous studies have shown estrogen receptors are localized in chondroid tissue of the condyle and retrodiscal tissue.[8] Estrogen depletion leads to serial degenerative changes in the TMJ, such as an increase in cartilage thickness or osteophyte formation.[9] Depending on the pain signaling type, estrogen action might be pro- or anti-nociceptive.[10] Estrogen increases the excitability of nociceptive afferents in the TMJ and masseter muscle.[11–14] The studies conducted by Cairns et al[11,14] found that glutamate excites putative nociceptive afferents within the TMJ and evokes nociceptive responses in the masseter muscle to a greater degree in female rats than in male rats, and increased glutamate concentrations sensitize the TMJ to noxious chemical stimuli.[13] While changes in peripheral afferent excitability after the application of glutamate are not produced indirectly as a result of inflammation,[12] there are gender-related differences in glutamate-evoked

jaw muscle activity that are dependent on estrogen. Gender-related differences in N-methyl-D-aspartate (NMDA) are also associated with NMDA-evoked rat masseter muscle afferent discharge.[15]

Several studies have reported variations in daily pain severity ratings in regularly cycling women, with pain levels reaching their maximum during menses and at the midluteal phase.[16–18] Dao et al[16] found significant variability in pain severity among naturally cycling patients compared to those on oral contraceptives, suggesting that pain severity stabilizes when the effect of hormonal fluctuations is minimized, while LeResche et al[17] suggested that TMD pain in women is highest at the time of the lowest estrogen and that rapid estrogen change put them at a higher risk of experiencing pain. Isselée et al[18] showed that pressure pain threshold variations of the masseter muscle in TMD myalgia patients were highest during follicular and luteal phases and lowest during the perimenstrual phase. According to the results of a study evaluating the effects of hormonal replacement therapy (HRT) on TMD in postmenopausal women, the pain intensity was higher among the women receiving HRT compared to those not receiving it.[19]

From the above studies and others, it appears that pain varies across the menstrual cycle, with the greatest sensitivity being when estrogen levels are low.[17–21] However, the systematic literature review recently conducted by Berger et al[7] did not find strong evidence to support the hypothesis that estrogen levels are associated with TMD, suggesting that the influence of estrogen on TMD seems to be multifaceted and that estrogen may influence TMD pain processing differently than TMJ structures. Therefore, the aim of this study was to evaluate whether serum estrogen level is associated with chronic pain, masticatory dysfunction, and depressive symptoms and/or somatization in women with TMD and different menstrual status.

Materials and Methods

Subject Selection

This study was conducted following approval given by the Institutional Ethics Committee of the Faculty of Medicine, University of East Sarajevo (Code No. 01-111-2). The study was conducted in accordance with the World Medical Association Declaration of Helsinki, as revised in 2008. The subjects gave their informed consent to participate in the study. The subjects were selected from those attending the Department of Gyneacology of the Foca University Hospital. A total of 125 women of 20 to 40 years of age who consulted their gynecologists for different reasons during the period from July 1, 2015 to July 31, 2016 were referred to the Department of Prosthetic Dentistry for TMD screening. Of those, 50 were normally cycling women, 45 were pregnant women, and 30 were women in surgical menopause.

The screening procedure was performed by two researchers using a brief questionnaire on difficulties with masticatory function (ie, chewing, swallowing, opening and closing the mouth) and experiencing TMD symptoms. A total of 67 women with positive screening results underwent a standardized clinical examination with the Research Diagnostic Criteria for TMD (RDC/TMD).[22] The diagnoses were generated according to Axis I.

The Graded Chronic Pain Scale on Axis II of the RDC/TMD was used to assess the severity of pain (worst pain in the past 3 months, average pain in the past 3 months, and pain right now), scored from 0 to 10. Depressive symptoms and somatization were assessed using The Symptom Checklist-90 (SCL-90 items)[23] included in Axis II of the RDC/TMD. Women were asked how often they had been distressed by each symptom. Items used a 4-point scale response format (0 [not at all], 1 [a little bit], 2 [moderately], 3 [quite a bit], and 4 [extremely]). The cut-off value for depression was < 0.535, moderate depression was defined as 0.535 to 1.105, and severe depressive symptoms were considered present if the score was greater than 1.105. The cut-off value for somatization was < 0.500, moderate somatization was defined as 0.500 to 1.000, and severe somatization was considered to be > 1.000.

The researchers provided the study participants with an invitation explaining the aims of the study and research protocol in order to facilitate understanding of the purpose of the study. Exclusion criteria were the use of oral contraceptives, muscle relaxants, and other medications; the use of oral appliances; metabolic diseases; neurologic disorders (eg, trigeminal neuralgia); and recent facial or cervical trauma.

Those who expressed interest in participating in the study were referred to a laboratory to obtain blood samples for further analysis. According to their menstrual cycle status, respondents were allocated into one of three groups: normally cycling women (Group 1), pregnant women (Group 2), and women in surgical menopause (Group 3). Initial screening criteria for TMD were not met in 44% of the women in Group 1, 49% in Group 2, and 57% in Group 3.

Laboratory Determination of the Level of Serum Estradiol

A volume of 2 mL of blood was drawn from each respondent according to the following:

- Normally cycling women (Group 1): The 6th day of follicular phase

- Pregnant women (Group 2): At the 4th, 12th, 24th, and 36th weeks of pregnancy
- Women in surgical menopause (Group 3): At the follow-up visit to the gynecologist

The blood sample was put into a tube without anticoagulant for serum separation. Serum separation was done by centrifuging the clotted blood samples at 1,800 rpm for 20 minutes, and the sample was immediately frozen at −20°C. The level of estradiol was determined by using the immunofluorescent method (AXSYM Estradiol Reagent Pack and Abbott AXSYM System). The results were analyzed using the ng/mL unit for estradiol. Analyses were carried out at the Biochemistry Department, University Hospital Foca. Sampling was controlled by one of the researchers (N.I.).

Statistical Analyses

Statistical analyses were carried out by using Statistical Package for the Social Sciences (SPSS) version 17.0. To test for any difference in the mean age between groups, analysis of variance (ANOVA) was used. The Kruskal-Wallis test with post hoc comparisons via a series of Mann-Whitney U tests was performed to analyze significant differences between groups.

Relationships between pain, psychological variables, and levels of estradiol were examined by using Spearman correlation coefficients. The results represent statistical frequencies of different categories. A P value < .05 was considered to indicate statistical significance.

Results

Demographic Characteristics

A total of 67 women met the RDC/TMD criteria for an Axis I diagnosis, and 64 (95.5% respondent rate) agreed to participate in the study. Of these, 28 had a normal menstrual cycle and were assigned to Group 1, 23 were pregnant and assigned to Group 2, and 13 were in surgical menopause and assigned to Group 3.

The mean ± standard deviation (SD) age of the women was as follows: 24.08 ± 4.0 years in Group 1, 27.75 ± 4.7 years in Group 2, and 40.56 ± 2.8 years in Group 3. ANOVA showed a significant difference in the mean age between the groups (P = .009).

Distribution of TMD Subtypes

No statistically significant differences between groups were found in the distribution of muscle disorders (P = .326) or mixed subtypes of TMD (P = .815). Menopausal women had a significantly

Table 1 Distribution of TMD Subtypes Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women

TMD subtype	Natural (n = 28)	Pregnant (n = 23)	Surgical (n = 13)	$P*$
Myofascial	4	2	3	.326
Disc displacement	9	8	3	.043
Mixed	15	13	7	.815

*Chi-square test. P < .05 was considered significant.

lower frequency of disc displacement compared to other women (P = .043) (Table 1).

Chronic Pain Grade Distribution

Although no statistically significant differences were found in the distribution of TMD subtypes, significant differences in pain intensity occurred. Post hoc analysis revealed that reported pain decreased with the progress of pregnancy among women from Group 2 and that it was the lowest at the 36th week (P < .001). Women in surgical menopause reported higher pain intensity (grades III and IV) compared to normally cycling women and pregnant women (P < .001 for both) (Table 2).

Limitation of TMD-Related Masticatory Function

No differences in difficulties when drinking, smiling, yawning, swallowing, or talking were detected between groups (P > .05). However, a significantly higher number of women in surgical menopause reported difficulties with chewing (P = .038), eating hard food (P = .023), and eating soft food (P = .049) compared to the normally cycling women and to women in the third trimester of pregnancy (Table 3).

Correlations Between Serum Estradiol Concentration and Chronic Pain, Depressive Symptoms, and Somatization

The distribution of respondents according to the severity of depressive symptoms and somatization is presented in Tables 4 and 5. The relationship between estrogen status and depressive symptoms/somatization was significant in all groups except for during the 4th week of pregnancy (P = .099 and P = .555, respectively). Further analysis showed that depressive symptoms and somatization were lowest among the women with advanced pregnancy (P < .001) and highest among menopausal women (P < .001). A statistically significant difference in the severity of depressive symptoms and somatization was also found between menopausal and normally cycling women (P = .042 and P = .011, respectively).

Table 2 Chronic Pain Grade Distribution According to Research Diagnostic Criteria for TMD (RDC/TMD) Axis II Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women

	Chronic pain grade										
Groups	0	I	II	III	IV	P^a			P^b		
G1: Natural (n = 28)							G1:G2 (4 wk)	G1:G2 (12 wk)	G1:G2 (24 wk)	G1:G2 (36 wk)	G1:G3
	7	8	8	4	1		.231	**.002**	**< .001**	**.001**	**< .001**
G2: Pregnant (n = 23)							4 wk:12 wk	4 wk:24 wk	4 wk:36 wk		
4 wk	7	7	6	2	1	.714	**.023**	**.015**	**< .001**		
12 wk	13	6	4	0	0	**.022**					
24 wk	17	5	1	0	0	**.002**					
36 wk	23	0	0	0	0	**< .001**					
G3: Surgical (n = 13)							G2 (4 wk):G3	G2 (12 wk):G3	G2 (24 wk):G3	G2 (36 wk):G3	
	2	4	3	2	2		**.016**	**.026**	**.011**	**< .001**	

G1 = Group 1; G2 = Group 2; G3 = Group 3. ^{a}Kruskal-Wallis test. ^{b}Post hoc comparisons via series of Mann-Whitney U tests.
Significant values (P < .05) are in bold.

Table 3 Limitation of Masticatory Function Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women

Limitation in masticatory function	Groups			
	Natural n = 28	Pregnancy^a n = 23	Surgical n = 13	P^b
Chewing				
Yes	10	6	9	**.038**
No	18	17	4	
Drinking				
Yes	8	5	3	.799
No	20	18	10	
Eating hard foods				
Yes	9	6	7	**.023**
No	19	17	6	
Eating soft foods				
Yes	2	6	5	**.049**
No	26	17	8	
Smiling/laughing				
Yes	1	2	0	.467
No	27	21	13	
Yawning				
Yes	3	3	0	.429
No	25	20	13	
Swallowing				
Yes	3	0	0	.144
No	25	23	13	
Talking				
Yes	2	0	0	.257
No	26	23	13	

^{a}Assessments were conducted in the 36th week of pregnancy.
^{b}Kruskal-Wallis test. Significant values (P < .05) are in bold.

The mean serum estradiol concentration in Group 1 was 0.10 ng ± 0.02 ng/mL. The highest mean concentration of serum estradiol (14.67 ± 0.45 ng/mL) was measured at the 36th week of pregnancy, and the lowest (0.02 ± 0.01 ng/mL) was measured in women in surgical menopause. The level of estradiol rose steeply over the course of pregnancy.

Higher chronic pain was associated with lower estradiol levels measured at the 4th ($\rho = -0.826$, P < .001), 12th ($\rho = -0.945$, P < .001), 24th ($\rho = -0.802$, P < .001), and 36th ($\rho = -0.803$, P < .001) weeks of pregnancy, and also in women in surgical menopause ($\rho = -0.983$, P < .001), but the correlation between these two variables was not statistically significant among the normally cycling women ($\rho = -0.354$, P = .054). A similar pattern was found for depressive symptoms and somatization. Statistically significant correlations were not detected between serum estradiol concentration and depressive symptoms (P = .207) or between serum estradiol concentration and somatization in Group 1 (P = .076); however, in Groups 2 and 3, correlations between serum estradiol concentration and depressive symptoms (P < .001), as well as between serum estradiol concentration and somatization (P < .001), were statistically significant (Table 6).

Discussion

The current study has found that the highest chronic pain grades were reported by women in surgical menopause. The results showed an increase in TMD-related pain associated with lower estrogen levels and an increase in pain reduction associated with higher estrogen levels during pregnancy. Although no differences were observed in drinking, smiling, yawning, swallowing, or talking, women in menopause experienced more difficulties with masticatory performance (chewing and eating hard and soft foods) compared with the normal cycling and pregnant women.

Other studies have also analyzed the relationship between estrogen levels and TMD, but their results are contradictory. Studies by Dao et al,[16] LeResche et al,[17,24] and Sherman et al[25] reported that TMD pain was associated with low estrogen levels, while studies by Landi et al[26,27] found that high estrogen levels

Table 4 Distribution of Respondents Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women According to the Severity of Depressive Symptoms

Groups	Depressive symptoms			P^a	P^b				
	None	Moderate	Severe						
G1: Natural (n = 28)					G1:G2 (4 wk)	G1:G2 (12 wk)	G1:G2 (24 wk)	G1:G2 (36 wk)	G1:G3
	13	9	6		.870	**.023**	**< .001**	**< .001**	**.042**
G2: Pregnant (n = 23)					4 wk:12 wk	4 wk:24 wk	4 wk:36 wk		
4 wk	10	8	5	.099	**.047**	**.015**	**< .001**		
12 wk	12	8	3	**.016**					
24 wk	15	7	1	**< .001**					
36 wk	20	3	0	**< .001**					
G3: Surgical (n = 13)					G2 (4 wk):G3	G2 (12 wk):G3	G2 (24 wk):G3	G2 (36 wk):G3	
	2	5	6		**.016**	**.042**	**< .001**	**< .001**	

[a]Kruskal-Wallis test. [b]Post hoc comparisons via series of Mann-Whitney U tests. Significant values ($P < .05$) are in bold.

Table 5 Distribution of Respondents Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women According to the Severity of Somatization

Groups	Somatization			P^a	P^b				
	None	Moderate	Severe						
G1: Natural (n = 28)					G1:G2 (4 wk)	G1:G2 (12 wk)	G1:G2 (24 wk)	G1:G2 (36 wk)	G1:G3
	14	9	5		.669	**.036**	**< .001**	**< .001**	**.011**
G2: Pregnant (n = 23)					4 wk:12 wk	4 wk:24 wk	4 wk:36 wk		
4 wk	9	7	7	.555	**.047**	**.015**	**< .001**		
12 wk	16	4	3	**.007**					
24 wk	18	4	1	**< .001**					
36 wk	21	2	0	**< .001**					
G3: Surgical (n = 13)					G2 (4 wk):G3	G2 (12 wk):G3	G2 (24 wk):G3	G2 (36 wk):G3	
	2	4	7		**.016**	**.017**	**< .001**	**< .001**	

[a]Kruskal-Wallis test. [b]Post hoc comparisons via series of Mann-Whitney U tests. Significant values ($P < .05$) are in bold.

Table 6 Correlations Between Serum Estradiol Concentration and Chronic Pain, Depressive Symptoms, and Somatization Among Normally Cycling (Natural), Pregnant, and Surgical Menopausal Women

Variable	Groups					
		Pregnancy				
	Natural	4 wk	12 wk	24 wk	36 wk	Surgical
Chronic pain						
ρ	−0.354	−0.826	−0.945	−0.802	−0.803	−0.983
P	.054	**.001**	**.001**	**.001**	**.001**	**.001**
Depressive symptoms						
ρ	−0.246	−0.627	−0.831	−0.808	−0.979	−0.920
P	.207	**.001**	**.001**	**.001**	**.001**	**.001**
Somatization						
ρ	−0.340	−0.729	−0.636	−0.744	−0.894	−0.954
P	.076	**.006**	**.001**	**.007**	**.001**	**.001**

Significant values ($P < .05$) are in bold.

increased TMD-related pain. Also of relevance are findings that estrogen has an effect on matrix composition in TMJ fibrocartilage and that lack of estrogen can induce pathologic changes in the TMJ, influencing the synovial membrane through its effect on the collagen and protein content of the TMJ disc.[28,29] On the other hand, the chondroprotective effects of estrogen may occur in the articular chondrocytes. Locally produced estrogen has been proven to contribute greatly to the function of cartilage by stimulating proliferation of chondrocytes and protecting them from spontaneous apoptosis,[30,31] which can lead to the onset of osteoarthritis.[32] This might explain why the low estrogen level affected not only the chronic pain grade but also masticatory function in women in surgical menopause. The difference in age between the groups could also potentially have influenced this finding.

While TMD has been included in dysfunctional pain syndromes characterized by abnormal central sensitization and pain modulation deficiency, TMD also belongs to a group of disorders that have been termed "affective spectrum disorders" due to an association with psychological distress.[33] Pain is acknowledged as being a causative or aggravating factor in the development of depressive symptoms, while depression, stress, and somatization have been reported to induce muscle hyperactivity, fatigue, and spasms, as well as occlusal disharmony and degenerative TMJ changes.[34,35] Patients with myofascial pain associated with osteoarthritis or arthralgia present with higher scores of depressive symptoms and somatization than patients diagnosed with other TMD subtypes. The development of pain and psychophysical symptoms associated with abrupt hormonal changes, as found in the current study, could be explained by a bidirectional influence of estrogen on the responses of a stress- and pain-modulatory system.[36] Instead of following the normal decline in hormonal output as seen in natural menopause, surgical menopause may cut off entirely the ovarian contribution to total hormone levels. If hormonal changes and fluctuations exert a psychophysical destabilizing action during certain female life cycle–related events, estrogen balance could be helpful in the prevention or treatment of TMD.[37] An interaction between estrogen and brain-derived neurotrophic factor (BDNF) begins an important molecular cascade to modulate the function of the hippocampus, which could potentially be responsible for the antidepressant effects of estrogen.[38] Nonetheless, it is unknown if hysterectomy itself, general anesthesia, or endotracheal intubation could have any effect on the pathogenesis of TMD pain and masticatory dysfunction.[39]

The development of TMD pain and psychophysical symptoms associated with abrupt hormonal changes, as found in the current study, could be explained by the complex activity of estrogens in TMD, including their immune (inflammatory), skeletal (bone deposition), and nervous system effects.[40] Numerous clinical studies have shown that increased levels of different cytokines (such as interleukin-1β [IL-1β], interleukin-6 [IL-6], interleukin-8 [IL-8], and tumor necrosis factor-α [TNF-α], as well as interferon-γ [IFN-γ], a T helper 1 [Th1] cytokine) in the synovial fluid of patients are associated with inflammation of the TMJ.[41] By stimulating endogenous ATP and subsequent activation of purinergic homomeric P2X3 and heteromeric P2X2/3 receptors, these cytokines are responsible for articular pain through an indirect sensitization of primary afferent nocireceptors.[42] TMJ inflammation is followed by production of numerous other mediators associated with TMD pain, among which prostaglandin E2 (PGE2) seems to play perhaps the most important role.[43–45]

The effects of estrogens on inflammatory and immune responses are very complex, and many pro- and anti-inflammatory activities are overlapping. Low levels of estrogens facilitate the pro-inflammatory response, including Th1-mediated mechanisms, whereas high levels of estrogen, such as those achieved during pregnancy, promote an anti-inflammatory T helper 2 (Th2) cytokine response.[46] These findings are in accordance with current and previous results[12] showing that TMD pain intensity decreased over the course of pregnancy and parallel the results of prior studies showing lower pain when estrogen levels are relatively high. Previous studies have suggested that clinical pain improvement in pregnancy could be attributable not only to dramatic changes in estrogen, but also to changes in progesterone. Estrogen increases the laxity of the TMJ, which may play an important role in the development of TMD.[34]

A number of studies have been designed to study the mechanisms by which estrogens modulate pain during TMD and show that the estrogen-TMD relationship is clearly not a simple one.[40] In the context of such complexity, the role of opioid receptors seems to be very important, as low levels of estrogens in the rat TMJ following experimentally induced inflammation are associated with greater responses to kappa opioid receptors and subsequent nociceptive behavior.[36,47,48]

The greater TMD pain observed in cycling women at ovulation or in postmenopausal women receiving HRT may be explained by both NMDA and non-NMDA excitatory amino acid (EAA) receptor types, which are located within the TMJ region and possibly contribute to jaw muscle activity that can be reflexively evoked from the TMJ region.[13,25] The gender-related differences in NMDA-evoked masseter muscle afferent discharges are considered to be due to an estrogen-mediated increase in expression of peripheral NMDA receptors by masseter ganglion neurons.[15] As Cairns et al have previously shown, the sensitivity of peripheral excitatory amino acid receptors is also related to the glutamate-evoked jaw muscle activity. Gender-related differences in glutamate-evoked afferent activity could involve either increased expression of excitatory amino acid receptors or augmentation of their function secondary to increased estrogen levels.[12,14] On the other hand, the activation and peripheral sensitization in some deep craniofacial nociceptive afferents involved in TMD may be modulated by the interaction mechanism of peripheral glutamate and capsaicin receptors.[49] Changes in the intrinsic properties of TMJ afferents could also be amplified by the presence of inflammatory mediators. The combined influence of estrogen and inflammation may contribute to the profound differences in TMD pain frequency and the severity pattern between genders.[50] It is noteworthy that predisposition to TMD is

dependent on the polymorphisms in estrogen receptor alpha (Erα), where the [GC] haplotype in the Xbal locus of ERα may increase the susceptibility to the disorder.[51]

The present study had several limitations. The sample size was small in all three groups, so the data need to be substantiated in larger studies. Normally cycling women were selected on the basis of regular periods, and the measurement of estradiol was restricted to the follicular phase of the menstrual cycle, when estrogen secretion increases gradually; therefore, whether pain peaks at different phases of the menstrual cycle could not be analyzed in the present study. It also must be noted that there was a significant age difference among the observed groups. As the women in Group 3 were older in comparison to the other two observed groups, it is reasonable to consider the possibility that the difference in age may emerge as a potential reason for the statistically significant differences found in the study. Additional research is needed to investigate the responses of TMD-related pain and associated symptoms to the hormonal changes caused by natural menopause.

Conclusions

TMD signs and symptoms may be modulated and sustained by estrogen levels. TMD-related chronic pain grade, masticatory dysfunction, depressive symptoms, and somatization improved over the course of pregnancy. Surgical menopause plays an important role in the development of TMD. Regulating the level and variations of estrogen across the hormonal cycle could be a promising approach for the treatment of TMD.

Acknowledgments

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