ORIGINAL ARTICLE

Effects of oral contraceptives on the treatment for internal derangements in temporomandibular joints in women

Jolanta Kostrzewa-Janicka [1], Bronisława Pietrzak [2], Piotr Jurkowski [1], Mirosław Wielgoś [2], Małgorzata Binkowska [3], Elżbieta Mierzwińska-Nastalska [1]

1 Department of Prosthodontics, Medical University of Warsaw, Poland
2 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
3 Department of Medical Centre Postgraduate Education, Warsaw, Poland

Correspondence to: Elżbieta Mierzwińska-Nastalska, PhD.
Departament of Prosthodontics, Medical University of Warsaw,
Nowogrodzka 59, pavillon XIa, 02-006 Warszawa, Poland.
tel: +48 22 502 18 86; e-mail: emierzw@amwaw.edu.pl

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Abstract

OBJECTIVE: The prevalence of signs and symptoms of temporomandibular disorders (TMD) is the highest among women of reproductive age. Estrogens are the major contributor to the regulation of bone growth and development. They also influence peripheral and central mechanism of pain. The aim of this study was to evaluate the efficacy of conservative treatment of temporomandibular joint (TMJ) internal derangements in regular cycling women with and without use of oral contraceptives (OCs).

MATERIAL & METHODS: The study included 229 women with TMJ disk displacement with and without reduction (DDwR and DDw/oR). The study group consisted of 191 normally cycling women and 38 women using combined OCs (COCs). The conservative TMD treatment was applied and its efficacy was rated during check-up visits.

RESULTS: The decreased odds of obtaining any or sufficient improvement during control visits were observed in women treated for DDwR and taking COCs for less than 3 years (p=0.01). There was a 2.7-fold higher risk for the failure of treatment in women taking COCs for less than 3 years during control visits in both diagnoses, DDwR or DDw/oR (p=0.082). There was investigated an increase in the risk for the lack of sufficient post-treatment improvement in diagnosed DDwR or DDw/oR in women with co-occurrence general osteoarticular lesions (p=0.07, p=0.04).

CONCLUSIONS: A worse TMJ internal derangements treatment efficacy was observed in women taking COCs for rather short time (less than 3 years) and in women with disorders in the osteoarticular system, what indicates modification of therapeutic procedures in that groups of patients.

Abbreviations:

COCs	- combined oral contraceptives	ID	- internal derangements
DDwR	- disk displacement with reduction	NCW	- normally cycling women
DDw/oR	- disk displacement without reduction	OCs	- oral contraceptives
EE	- 17β-ethynyloestradiol	RDC/TMD	- Research Diagnostic Criteria for Temporomandibular Disorders
EP1	- main end point	TMD	- temporomandibular disorders
EP2	- secondary end point	TMJ	- temporomandibular joint

INTRODUCTION

Temporomandibuar disorders (TMD) are responsible for frequent pain and dysfunction conditions, which affect temporomandibular joint (TMJ) and/or masticatory muscles (Dworkin & Le Resche 1992). The highest TMD prevalence is diagnosed in women in their reproductive years (Dworkin *et al.* 1990). The gender difference in TMD indicates the role of sex hormones in the generation of the signs and symptoms of this disorder (Le Resche 1997), especially, when the pain suffered is taken into consideration (Cairns & Gazerani 2009). It is revealed that women suffer more frequent and more severe pain than men. In many cases the pain is anatomically diffused and chronic (Unruh 1996). There are two female hormones, estrogen and progesterone, examined in cases of musculoskeletal pain. However, the majority of studies have revealed that estrogens influence peripheral and central mechanisms of pain (Smith *et al.* 2006), and the increase and decrease in estrogen levels during menstruation are linked with increased TMD pain (Le Resche *et al.* 2003). It is suggested that female reproductive hormones may play an etiologic role in orofacial pain, but they may also affect the bone and the articular cartilage, and could contribute to a higher incidence and prevalence of inflammation of the gingival tissues (Le Resche 1994; Le Resche 1997a; Le Resche 1997b; Unruh 1996; Talwar *et al.* 2006; Cassorla et a. 1984; Straka 2011).

The aim of that study was to assess the efficacy of conservative treatment of TMJ internal derangements (ID) in regular cycling women with and without use of oral contraceptives (OCs).

MATERIAL AND METHODS

A group of 229 women, aged 18–45 years (mean, 30.05±6.98), diagnosed with the signs and symptoms of TMJ internal derangements, according to the Research Diagnostic Criteria for Temporomandibular Disorders, (RDC/TMD, (Dworkin & Le Resche 1992)), with regular menstruation, was eligible for the study. The observed TMJ disk displacement from its position between the condyle and the eminence to an anterior and medial or lateral position, but reduced on full opening, usually resulting in a noise (reciprocal clicking), justified our diagnosis of disk displacement with reduction (DDwR), (group IIa, according to RDC/TMD). The condition in which the disk was displaced from normal position to anterior and medial or lateral, associated with limited mandibular opening, allowed us to diagnose disk displacement without reduction (DDw/oR), (group IIb, according to RDC/TMD).

The adopted exclusion criteria comprised the presence of irregular cycling, nonspecific clinical symptoms, psycho-emotional disorders, mental diseases and smoking.

Finally, based on the study inclusion and exclusion criteria, the study group consisted of 162 (70.74%) women with DDwR and 67 (29.26%) with DDw/oR. This group comprised 191 (83.41%) normally cycling women (NCW), menstruation every 28±3 days, and 38 (16.59%) women using OCs. OCs were applied in combined (monophasic, low dose, binary) pills containing estrogen (17β-ethynyloestradiol), (EE) in a dose of 20–35 mcg and different types of progestagen. Combined oral contraceptives (COCs) were applied according to a typical regime of 21 days of active pills followed by the 7-day hormone-free interval.

The study was approved by the University Human Ethics Committee. An observational, prospective study has been designed with two end point evaluations, main – the failure of treatment (EP1) and secondary – the lack of sufficient post-treatment improvement (EP2). The condition with pain decrease, but still present signs and symptoms of the dysfunction (TMJ sounds during mandibular movements or/and impaired mandibular movements) was regarded as a failure of treatment. The sufficient improvement was claimed when no pain complaints and the silent decrease dysfunction symptoms (sporadic TMJ sounds or/and slight mandibular movement disturbances) were observed. Both end points were assessed two and six weeks after the applied treatment (control visits I and II).

The following factors with potential to determine the achievement of end points were identified: the patients' age, progression of the dysfunction (DDwR or DDw/oR), duration of complaints, co-occurrence of general medical disorders and use of OCs The dysfunction progression phase applied to disk displacement with or without reduction according to RDC/TMD.

On physical examination the data concerning age, duration of complaints, general medical disorders, menstrual cycling, as well as duration of use and type of hormonal contraceptives, were obtained. The duration of temporomandibular pain condition was assessed as short-term (no longer than 6 months on average); medium-term (from 7 months to 3 years); and long-term (over 3 years).The duration of contraceptive use was defined as medium (less than 3 years) and long-term (over 3 years)

TMD treatment management in the study group of women involved the following procedures: anti-inflammatory (non-steroids drugs), TMJ unload (occlusal splints: stabilization or repositioning), muscles relaxation (muscle stretch by stabilization splint), and supplementary management (vitamins C, A and E, glucosamine, chondroitin sulfate).

During check-up visits the treatment efficacy was rated as follows: failure of treatment, when were no or minor improvement, and sufficient improvement. Control visits followed the same scheme as that employed during the diagnostic visit, according to axis I of the RDC/TMD clinical examination.

Statistics

Statistical analysis was performed using logistic regression to assess relations between factors of interest and endpoints of this study. The strength of association was expressed by means of odds ratio and 95% confidence interval. For this reason quantitative factors were categorized. Only for age odds ratios were expressed per 10 years. In addition to one factor analyses adjustment for suffering duration was performed (series of two factors analyses). All tests have two-sided *p* values and 0.05 was considered as significance. SAS System was used to calculations (SAS/STAT User's Guide 12.1, 2012). The methodology was based on van Belle *et al.* 2004.

RESULTS

Temporomandibular dysfunction lasting over 3 years was found in 50 (23.81%) women of the study group (Table 1). The co-occurrence of other diseases and general medical disorders was diagnosed in 106 (46.29%) women. Rheumatic disease and different skeletal disorders were observed in 23 (10.04%) women. Of the 38 women taking oral contraceptives, 21 (55.26%) patients used COCs for less than 3 years and 17 (44.74%) for over 3 years.

Following the treatment of TMJ internal derangement, 88.64% of patients showed post-treatment improvements during both control visits. The lack of sufficient improvement was recorded in 16.59% of patients during visit I and in 15.72% of patients during visit II (EP2), whereas the failure of treatment (EP1) was noted in 11.35% of patients during visits I and II.

The one-factor analysis showed that the risk for the failure or lack of sufficient improvement was similar in the women diagnosed with DDwR or with DDw/oR during both visits (Tables 2 and 3). No relationship was observed between treatment failure and the patient's age, duration of complaints or co-occurrence of general medical disorders. However, there was a 2.5-fold increase in the risk for the lack of sufficient post-treatment improvement in women with co-occurring diseases of the osteoarticular system in both diagnoses, DDwR or DDw/oR, during visits I and II; (OR=2.47; 95%Cl=0.94–6.49; p=0.067; OR=2.67; 95%CI=1.01–7.05; p=0.047). The one-factor analysis of the risk for reaching the identified end points revealed significant decrease odds of obtaining any improvement during visits I and II only in patients treated for DDwR and taking oral contraceptives for less than 3 years (p=0.01). Saliently decreased odds of obtaining a sufficient improvement was also recorded in this group of women during visits I and II (p=0.05; p=0.03). On the verge of significance was a 2.7-fold higher risk for the failure of treatment in women diagnosed with both DDwR and DDw/oR and taking COCs for less than 3 years during visits I and II (OR=2.67; 95%CI=0.88–8.08; p=0.082) in diagnosed both, DDwR or DDw/oR.

Tab. 1. Baseline characteristics.

	% (n)	x±SD
Internal derangement		
DDwR	70.74 (162/229)	
DDw/oR	29.26 (67/229)	
Age	18–45 years	30.05±6.98
General disorders*	46.29 (106/229)	
Suffering duration		
≤6 months	39.52 (83/210)	
6 months–3 years	36.667 (77/210)	
>3 years	23.81 (50/210)	
Oral contraceptive duration		
No	83.41 (192/229)	
< 3years	9.17 (21/229)	
≥3 years	7.42 (17/229)	
Skeletal disorders	10.04 (23/229)	

*often infections in upper respiratory tracks (2.6%), allergy (10.0%), bronchial asthma (3.0%), icterus typeB (0.4%), irritable colon syndrome (0.4%), gastric ulcer (1.3%), gastric inflammation (2.1%),multiple sclerosis (0.4%), migraine (2.1%), diabetes (0.4%), anemia (0.4%), arterial hypertension (2.1%),circulatory insufficiency (2.5%), fatty degeneration of the liver (0.4%), temporal lobe epilepsy (0.4%).

The two-factor analysis of data, adjusted for suffering duration, revealed significant increasing the risk of failure of treatment (EP1), during visits I and II in women taking COCs less than 3 years (OR=3.37; 95%CI=1.08–10.6 p=0.03). It was observed not significant increased risk for not obtaining the sufficient improvement (EP2) regardless of time of suffering duration in women taking the COCs less than 3 years during visits I and II (OR=2.04; OR=2.14) The analysis of women with the_osteoarticular system disorders showed in this group of patients almost three-fold decrease in the odds of obtaining sufficient improvements (EP2) during both control visits (OR=2.67, p=0.05; OR=2.79, p=0.04) regardless of time of suffering duration. The two-factor analysis, adjusted for the patients' age and ID type (DDwR or DDw/oR) showed the results similar to those obtained in the one-factor analysis (Tables 2 and 3).

The interpretation of the results should take into account some study limitations, such as the lack of sex hormones examination during the physiological cycle before TMD treatment, the data on the suffering duration, the type and duration of oral contraceptives taken from the RDC/TMD questionnaire, and the magnetic resonance imaging performed only in severe ID cases.

Tab. 2. Risks of main and secondary endpoints depending on the factors of interest on the I visit.

	Risk of failure of treatment (EP1)					Risk adjusted for suffering duration		Risk of lack of sufficient improvement (EP2)					Risk adjusted for suffering duration	
	OR	95%		CI	*p*-value	OR#	*p*-value	OR	95%		CI	*p*-value	OR#	*p*-value
Age (per 10 years)	1.10	0.61	–	1.98	0.750	1.31	0.386	0.92	0.56	–	1.52	0.740	0.98	0.938
Age <25	1.00					1.00		1.00					1.00	
Age ≥25	1.09	0.41	–	2.86	0.862	1.31	0.610	0.89	0.40	–	1.97	0.770	0.92	0.836
DDw/oR vs DDwR	0.88	0.35	–	2.20	0.781	0.98	0.971	1.14	0.54	–	2.42	0.731	1.19	0.669
Suffering duration														
≤6 months	0.73	0.29	–	1.87	0.512	0,80	0.665	0.84	0.37	–	1.91	0.671	0.94	0.888
6 months – 3 years	1.00					1.00		1.00					1.00	
<3 years	0.52	0.16	–	1.74	0.290	0.43	0.302	0.86	0.33	–	2.22	0.751	0.65	0.507
General disorders														
Yes	1.18	0.52	–	2.68	0.687	1.19	0.686	1.05	0.52	–	2.12	0.884	1.12	0.767
No	1.00					1.00		1.00					1.00	
Oral contraceptives														
No	1.00					1.00		1.00					1.00	
<3 years	2.67	0.88	–	8.08	**0.082**	3.37	**0.037**	1.61	0.55	–	4.73	0.384	2.04	0.207
≥3 years	0.53	0.07	–	4.25	0.554	0.59	0.615	0.69	0.15	–	3.16	0.631	0.75	0.717
Skeletal disorders														
Yes	1.76	0.55	–	5.65	0.341	1.87	0.300	2.47	0.94	–	6.49	**0.067**	2.67	**0.050**
No	1.00					1.00		1.00					1.00	

Bold fonts were used for significance levels less then 0.05 and less then 0.10 for the verge of significance; OR – crude odds ratio; OR# – odds ratio adjusted for suffering duration

DISCUSSION

The population-based epidemiological studies highlight a growing number of people seeking treatment for TMJ disorders (Mcflane *et al.* 2001). Women of reproductive age make the highest percentage in this group of patients (Dworkin *et al.* 1990; Le Resche 1997a). Due to the applied treatment the improvements were obtained in 88.64% of patients. Similar assessment rates of the conventional treatment efficacy in ID cases have been reported by other authors (Ekberg & Nilner 2006; Okeson 1988). No effects of DDwR or DDw/oR progression phase, duration of complaints and the patient's age on the possibility of achieving a positive treatment outcome was evidenced by the studies performed. However, different response to the applied treatment was revealed in women taking COCs. A 2.6-fold increase in the risk for the failure of treatment in women taking COCs for less than 3 years was recorded on the verge of significance. Although the analysis regardless of the suffering duration, showed a significant higher risk for the failure of treatment during visits I and II in women taking COCs for less than 3 years. Despite the fact that this analysis did not reveal the importance of the risk for not obtaining sufficient improvements during none of these two visits, the clinical importance is evidenced by a still high risk for the persistence of complaints in this group of patients should be taken into consideration (OR=2.04, OR=2.14). The more so because the analysis concerning the progression of the disorder (DDwR or DDw/oR) demonstrated a significantly higher risk for the occurrence of defined and points in women with DDwR and taking COCs for less 3 years.

Studies carried out by LeResche *et al.* (1997b) show more frequent medical visits because of TMJ disorders among women taking OCs. They also revealed that women with TMJ disorders report a higher pain intensity at lower levels of estrogens or their sudden fluctuations (Le Resche *et al.* 2003). Moreover, the results of our own study showed the effect of oral contraception also on the efficacy of treatment for TMJ disorders.

During the menstrual cycle the ovarian excretion of main estrogen, 17β-estradiol, rises gradually until ovulation then it falls and rapidly drops shortly before menses to rise again after it ends. If combined OCs, especially EE-contaning classic preparations, are used then the 17β-estradiol level remains low and stable and does not rise significantly during the 7-day hormone-

Tab. 3. Risks of main and secondary endpoints depending on the factors of interest on the II visit.

	Risk of failure of treatment (EP1)					Risk adjusted for suffering duration		Risk of lack of sufficient improvement (EP2)					Risk adjusted for suffering duration	
	OR	95%		CI	*p*-value	OR#	*p*-value	OR	95%		CI	*p*-value	OR	*p*-value
Age (per 10 years)	1.18	0.66	–	2.12	0.577	1.31	0.386	0.99	0.60	–	1.66	0.982	1.04	0.898
Age <25	1.00					1.00		1.00					1.00	
Age ≥25	1.09	0.41	–	2.86	0.862	1.31	0.610	0.97	0.42	–	2.20	0.933	1.05	0.916
DDw/oR vs DDwR	1.09	0.45	–	2.63	0.857	0.98	0.971	1.26	0.59	–	2.68	0.559	1.27	0.564
Suffering duration														
≤6 months	0.73	0.29	–	1.87	0.512	0.80	0.665	0.76	0.33	–	1.77	0.524	0.85	0.727
6 months–3 years	1.00					1.00		1.00					1.00	
<3 years	0.52	0.16	–	1.74	0.290	0.43	0.302	0.86	0.33	–	2.22	0.751	0.66	0.513
General disorders														
Yes	0.99	0.44	–	2.25	0.988	1.19	0.686	0.92	0.45	–	1.87	0.809	1.04	0.925
No	1.00					1.00		1.00					1.00	
Oral contraceptives														
No	1.00					1.00		1.00					1.00	
<3 years	2.67	0.88	–	8.08	**0.082**	3.37	**0.038**	1.75	0.59	–	5.14	0.312	2.14	0.181
≥3 years	0.53	0.07	–	4.25	0.554	0.59	0.615	0.75	0.16	–	3.43	0.705	0.79	0.758
Skeletal disorders														
Yes	1.76	0.55	–	5.65	0.341	1.87	0.300	2.67	1.01	–	7.05	**0.047**	2.79	**0.041**
No	1.00					1.00		1.00					1.00	

Bold fonts were used for significance levels less then 0.05 and less then 0.10 for the verge of significance; OR – crude odds ratio; OR# – odds ratio adjusted for suffering duration

free interval between taking OCs during which menstrual bleeding occur. It should be added that new OCs models have been introduced over recent 4 years. They contain estradiol valerate or synthetic estradiol as an estrogenic compound that provides a higher concentration of estradiol (30–65 pg/mL), characteristic of an early phase of proliferation, but they were not used in participants of this study.

It is likely that the difference in the level of the main estragon, 17β-estradiol, observed between women using classic OCs and NCW, has a causative relationship with pain suffered in TMJ disorders. In women who do not take OCs, the intensified pain induced by rapid fluctuations in the 17β-estradiol level may occur in the perimenstrual period, whilst in women using OCs its persistence is observed during the whole cycle (Le Resche 2003).

The mechanism by which sex hormones are implicated in the TMD pathology has not as yet been fully elucidated (Ribeiro-Dasilva *et al.* 2009; Abubaker *et al.* 1993; Le Resche *et al.* 1994). However, a causative role of sex hormones in the development of TMD has already been indicated, pointing at the same time to the intensified symptoms of this pathology at low estrogen concentrations and the effects of their fluctuation on the pain suffered. In this context the effect of exogenous hormonal therapy, involving contraceptives (blockage of endogenous hormone excretion) and hormone replacement therapy (supplementing the post-menopausal deficiency) is worth considering.

The results of the presented study may have significant clinical implications, e.g., attempts to apply unnecessary and more invasive therapeutic methods instead of consulting a gynecologist-endocrinologist to undertake a combined diagnostic, and therapeutic procedures. In such cases the application of contraceptives, containing another estrogen, estradiol or its valerate or other types of contraception, including hormonal contraception (progesterone mini-pill, intrauterine system releasing levonorgestrel) could be possible. This could possibly decrease pain perception, which may be partly dependent on the concentration of estrogens. This approach could eliminate an adverse influence of distinctly lower concentration of sex hormones in women taking OCs compared with NCW, as this may be the cause of poor response to the applied TMD treatment in this group of women. Interestingly, there are findings showing that the risk for treatment failure is the

same or even lower in women using OCs for a longer period of time (over 3 years) than in women with natural cycles. The explanation of this finding warrants further investigations. Great variations in metabolism of EE and progestin as a result of the so called effect of the first transit through the liver may play a role. This process undoubtedly affects the bioavailability of both OCs components and their bioactivity. A long-term use of OCs may alter both absorption and pharmacokinetics of applied hormones.

Similar negative effects on the efficacy of ID conservative treatment in women was found in the co-occurrence of TMJ internal derangement and diseases of the osteoarticular system. The impact of this factor with its potential to diminish the treatment efficacy was not dependent on women's age, type of TMJ internal derangement or use of COCs. However, the interpretation of this finding is disputable. General osteoarticular lesions are not always manifested in the TMJ region (Bjornland *et al.* 1994) and some attempts to explain this fact are primarily based on different TMJ histological structure (Minarelli & Liberti 1997; Salo & Raustia 1995). TMJ is a synovial joint but it differs in the type of connective tissues, which cover articular surfaces. Pathophysiology of lesions in the TMJ region is the same as that in other joints of the body (Kaneyama *et al.* 2005). This is confirmed, among others, by the investigations focused on the inflammatory mediators in the TMJ synovial fluid (Milam & Schmitz 1995; Kubota *et al.* 1998). However, the difference is observed when they occur, since the type of TMJ cartilage shows a considerable ability to induce reconstruction and regeneration. It may take a number of years before inflammatory and degenerative lesions in the TMJ region become visible in X-ray pictures. General disorders in the osteoarticular system may suggest that the body is predisposed to inflammations in joint connective tissues and thus to a diminished ability to promote regeneration and repair. Therefore, It seems advisable to consider the effect of such factors as occlusal disorders, parafunctions or orthodontic treatment for TMD. The coexistence of topical adverse effects and systemic pathology in the region of other joints may hinder the possibility of achieving the desired treatment outcome and implies a multidisciplinary approach.

The suggested mechanisms of pathologic changes (inflammation, degeneration, deformation) in the TMJ and major predisposing factors for TMJ pain and dysfunction are excessive loading, stress, estradiol fluctuations, alterations in the extracellular matrix and genetics (Stegenda *et al.* 1989; Milam & Schmitz 1995; Cairns 2010; Green 2001). The presented study also highlights the effect of simultaneous prevalence of general skeletal disorders and usage of exogenous sex hormones of oral contraceptives, as the modulating factors for treatment effectiveness, where indicated the different response to applied treatment dependent on the discussed factors.

CONCLUSIONS

The effective conservative treatment for TMJ internal derangement is feasible regardless of the duration of dysfunction, its degree of progression, patients' age and co-occurrence of general medical disorders.

A worse prognosis for ID treatment efficacy are observed in patients taking combined OCs for rather short time (less than 3 years), and in patients with disorders in the osteoarticular system.

It seems essential to consider the modification of therapeutic procedures if the internal temporomandibular joint disorders are diagnosed in women taking short-term combined OCs and/or in women with diagnosed general disorders in the osteoarticular system.

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