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Temporomandibular disorder and serum levels of progesterone and estrogen: Systematic review

Disfunção temporomandibular e níveis séricos de progesterona e estrogênio: Revisão sistemática

Disfunción Temporomandibular y niveles de progesterona y estrógeno en suero: Revisión sistemática

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Abstract
Temporomandibular Disorder (TMD) is a pathology of the stomatognathic system characterized by a set of clinical disorders that includes a temporomandibular joint, a masticatory musculature and associated structures. It is the most common orofacial pain condition of non-dental origin and which is increasing among adults in the age group between 18 and 45 years with a not well defined etiology, mainly not with regard to its higher prevalence in women than men. The present study aimed to evaluate the literature if there is a relationship between the levels of progesterone and estrogen with the clinical manifestations of TMD. The systematic search was carried out in the following electronic databases: PubMed, Web of Science, SciELO, and LILACS, Scopus, Embase and Google Scholar in addition to a complementary manual search of cross-references of original articles. There was no time restriction. The descriptors used were "TMD" or "TMJ" and "progesterone" and "estrogen". Initially, 132 articles were found, were 15 presented the eligibility criteria to be read in full. In the end, 4 studies were included in the review. The conclusion was that most studies relate the variations of progesterone and estrogen to the symptoms of the disease; however, there are differences between them. Thus, it is recommended to carry out studies that analyze this relationship, leading to hormonal fluctuations ranging from reproductive age to post-menopause.
Keywords: Temporomandibular dysfunction; Orofacial pain; Estrogen; Progesterone.

Resumo
A Disfunção Temporomandibular (DTM) é uma patologia do sistema estomatognático caracterizada por um conjunto de desordens clínicos que inclui a articulação temporomandibular, a musculatura mastigatória e estruturas associadas. É a condição de dor orofacial mais comum de origem não-dentária e que vem aumentando entre adultos na faixa etária entre 18 e 45 anos com etiologia não bem definida, principalmente no que diz respeito à sua maior prevalência em mulheres que homens. O presente estudo buscou avaliar através da literatura se há relação entre os níveis de progesterona e estrogênio com as manifestações clínicas da DTM. A busca sistemática foi realizada nas seguintes bases eletrônicas: PubMed, Web of Science, SciELO e LILACS, Scopus, Embase e Google Scholar, além de busca manual complementar de referências cruzadas de artigos originais. Não houve restrição de tempo. Os descritores

utilizados foram “TMD” ou “TMJ” e “progesterone” e “estrogen”. Inicialmente, 132 artigos foram encontrados, onde 15 apresentavam os critérios de elegibilidade para ser realizada a leitura na íntegra. Ao final, 4 estudos foram incluídos na revisão. Concluiu-se que a maioria dos estudos relacionaram as variações de progesterona e estrogênio com a sintomatologia da doença, entretanto, há divergências entre eles. Dessa forma, recomenda-se a realização de estudos que analisem essa relação levando as flutuações hormonais que vão desde a idade reprodutiva até a pós-menopausa.
Palavras-chave: Disfunção temporomandibular; Dor orofacial; Estrogênio; Progesterona.

Resumen
La disfunción temporomandibular (DTM) es una patología del sistema estomatognático caracterizada por un conjunto de trastornos clínicos que incluye la articulación temporomandibular, los músculos masticatorios y las estructuras asociadas. Es la condición de dolor orofacial de origen no dental más común y ha ido aumentando entre los adultos en el grupo de edad entre 18 y 45 años con una etiología no bien definida, principalmente en lo que respecta a su mayor prevalencia en mujeres que en hombres. El presente estudio buscó evaluar a través de la literatura si existe una relación entre los niveles de progesterona y estrógeno con las manifestaciones clínicas de TTM. La búsqueda sistemática se realizó en las siguientes bases de datos electrónicas: PubMed, Web of Science, SciELO y LILACS, Scopus, Embase y Google Scholar, además de una búsqueda manual complementaria de referencias cruzadas de artículos originales. No hubo restricción de tiempo. Los descriptores utilizados fueron "TMD" o "TMJ" y "progesterona" y "estrógeno". Inicialmente se encontraron 132 artículos, de los cuales 15 presentaron los criterios de elegibilidad para ser leídos en su totalidad. Al final, se incluyeron 4 estudios en la revisión. Se concluyó que la mayoría de los estudios relacionan las variaciones de progesterona y estrógeno con los síntomas de la enfermedad, sin embargo, existen divergencias entre ellos. Por ello, se recomienda realizar estudios que analicen esta relación, tomando fluctuaciones hormonales que van desde la edad reproductiva hasta la posmenopausia.
Palabras clave: Disfunción temporomandibular; Dolor orofacial; Estrógeno; Progesterona.

1. Introduction

Temporomandibular Dysfunction (TMD) is the term designated for a set of clinical disorders that includes conditions of the temporomandibular joint, masticatory muscles, and associated structures (Bartley & Fillingim, 2013). The symptoms described include limitation in mandibular movement, generalized and joint myofascial pain, presence of noise associated with the function, and functional limitation, locking or deviation of the mandible opening (De Rossi, Greenberg & Steinkeler, 2014). Its exact etiology is not yet well defined, but several studies related to stress and anxiety (Reiter *et al.*, 2015; Wieckiewicz *et al.*, 2014), as well as age, occlusion and parafunction (Shedden *et al.*, 2012), systemic inflammatory pathologies (Wahid *et al.*, 2014), such as rheumatoid arthritis (Benoliel & Sharav, 2010; Yu *et al.*, 2009) and gender (De Rossi, Greenberg & Steinkeler, 2014; Yu *et al.*, 2009).

It is the most common orofacial pain condition of non-dental origin, which has been increasing over time, affecting mainly the age group between 18-45 years, with a higher prevalence in women (in the proportion of 3: 1) than men. About 80% of treated patients are women. The pre-menopause period has a greater number of cases than the post-menopause (Bartley & Fillingim, 2013; Joseph *et al.*, 2019; Stinson *et al.*, 2019; Maurer *et al.*, 2016). The reason for this difference between genders is not clear, but it supports the study of female hormones - estrogen and progesterone - as a predisposing factor to the development and severity of the disease. In addition, clinical signs such as the presence of painful symptoms after puberty, the lower prevalence in post-menopausal years, and the reduction of symptoms during pregnancy reinforce this hypothesis (Wahid *et al.*, 2014; De Rossi, Greenberg & Steinkeler, 2014; Yu *et al.*, 2009).

Estrogen is a representative steroid hormone and is associated with several functions in the body systems in both sexes, including the development, restitution, and metabolism of the temporomandibular region and related structures, as well as pain mediation through the presence of its receptors (Kou *et al.*, 2011; Lu *et al.*, 2012; Torres-Chávez *et al.*, 2012). Studies show the high affinity of receptors present in the ATM, which influence the function and maintenance of these structures. Variations in estrogen hormone levels are able to promote sagging joints, especially during pregnancy, and this is believed to have a role in the development of some disorders (Patil *et al.*, 2015). Estrogens act on bone, promoting osteoclastic activity,

and cartilage influencing its renewal (Landi *et al.*, 2005). Inflammatory modulation occurs through the interaction between inflammatory mediators such as histamine, serotonin, platelet-activating factor, and nitric oxide, which act centrally and regionally, influencing bone, joint, and muscle pain (Patil *et al.*, 2015).

Progesterone is related to inflammatory and immunological modulation. Its reduction can induce an exacerbated inflammatory response and its maintenance at normal levels demonstrates a reduction in edema and pain in inflammatory diseases (Patil *et al.*, 2015; Xue *et al.*, 2017). Animal studies have shown a strong relationship between high levels of estrogen and inflammation of the temporomandibular joint through cytokine production (Kou *et al.*, 2011) and an improvement in symptoms caused by increased levels of progesterone (Xue *et al.*, 2017).

In addition, estrogens and progesterone can affect the content and characteristics of collagen fibers, both hormones, alone or in combination, increase the type III collagen content and lead to a decrease in type I / III collagen ratio (Madani *et al.*, 2013). Immunohistochemical analyzes demonstrated the presence of estrogen and progesterone receptors in the human articular disc, and higher requirements for estrogen receptors in the disc of women with TMD signs and symptoms. According to these authors, a concomitant presence of these receptors and specific levels of circulating hormones can lead to changes in the connective tissue of the TMJ disc, causing previous changes (Landi *et al.*, 2005).

A previous systematic review (Berger *et al.*, 2015) analyzed only estrogen and its relationship to pain processing in TMD, concluding that there is a need to conduct a study that analyzes its action on joint development, restitution, and metabolism, as well as its influence on regulatory mechanisms of pain.

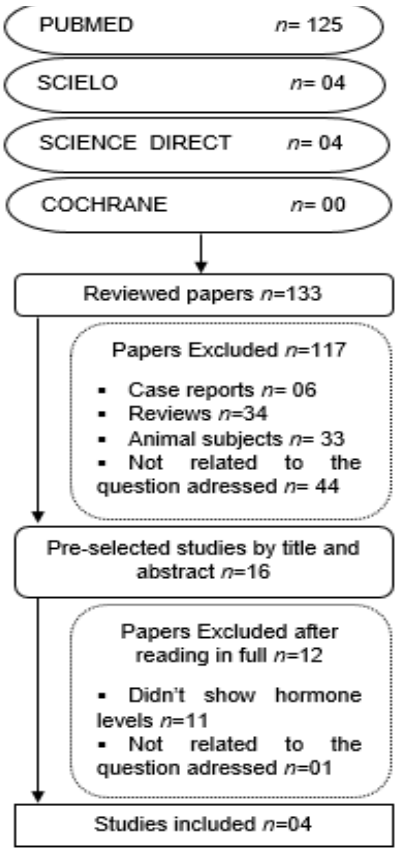
This systematic survey of the literature aims to assess whether the relationship between changes in serum levels of progesterone and estrogen with the development and intensity of TMD in women.

2. Methodology

This systematic review was carried out in accordance with the statements of preferred reporting items for systematic analysis and meta-analysis protocols (PRISMA-P), with guidance from the Cochrane Handbook for Systematic Reviews. The protocol of systematic review is registered in the Prospective International Register of Systematic Reviews (PROSPERO), under number CRD42020198880.

The material for our study consisted of publications identified by advanced search performed independently by two authors using the databases PubMed (MEDLINE), PMC (PubMed), Cochrane, SciELO and Science Direct. Searches were also carried out on the Scopus and Embase bases. Gray literature was also consulted through Google Scholar. In order to identify relevant publications, a search was performed using the descriptors "Estrogen", "Temporomandibular Joint Disorder" and "Progesterone", identified by means of Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). Boolean operators (AND and OR) were used to combine the descriptors and enhance the search strategy through different combinations. A manual search of cross-references of original articles was also carried out to identify additional studies that could not be located in the electronic databases. These procedures were performed to avoid possible selection and publication bias. The search

Figure 1. Search strategy.



Source: Illustrations made by the authors themselver (2021).

strategy is illustrated in the flowchart (Figure 1).

Data collection was carried out independently by two reviewers (RFFS and BDS), in three different phases. First, the reviewers discussed the eligibility criteria, in order to assess possible errors in the method. Then, the titles were read carefully to exclude articles outside the scope of this research. Studies in which the subject of interest could not be addressed were excluded. In phase 2, the abstracts of the other studies were analyzed independently by the two reviewers. At this stage, abstracts were excluded in which the subject of interest could not be addressed, literature reviews, case reports, animal and/or in vitro studies and studies without quantitative assessment of hormone levels. Inter-examiner agreement was assessed using the Kappa statistic, with a total of 10% and 90% of the studies evaluated in phases 1 and 2, obtaining a strong agreement ($K \geq 1.00$ and $K \geq 0.95$), respectively, confirming the reproducibility and reliability of the evaluation. In phase 3, the other articles had their full text evaluated and their reference lists were carefully read to identify studies that could not be located. Then, the articles were evaluated to see if they met the other eligibility criteria. Studies in which the relationship between hormonal variations and TMD were not measured using quantitative serological tests were excluded. After evaluation, 4 studies were included. In situations where a mutual agreement was not reached between the two reviewers, a third reviewer (JRCQ) was involved to make a final decision. The rejected studies and the reasons for their exclusion were recorded in Table 1.

Table 1. List of Excluded Studies.

REASON FOR EXCLUSION	FIRST AUTHOR
Case reports	Aneiros-Guerrero et al. 2011; Soni et al.2018; Kayipmaz et. al., 2019; Koumarianou et. al., 2016; Stefanaki et. al., 2020; Rohan et. al., 2014.
Reviews	Fietz, 2018; Stinson et al. 2019; Farage, 2010; Lee et al. 2017; Sinno et al. 2011; Johnston et. al., 2015; Lucaccioni et. al., 2020; Chukhlovin, 2015; Dussor et. al., 2018; Ratner et. al., 2019; Casarini et. al., 2011; Szymańska et al., 2018; Landomiel et. al., 2019; Zhou et. al., 2019; Aniogo et. al., 2019; Lee & Judge, 2017; Roi et. al., 2019; Pani et. al., 2010; Pasquier et. al., 2014; Al-Bashaireh et. al., 2018; Jones & George, 2014; Ulloa-Aguirre et. al., 2018; Janeček & Dabrowska, 2019; Jani et. al., 2014; Kanherkar et. al., 2017; Detamore et. al., 2007; Köck et. al., 2007; Rogers, 2009; Al et.al., 2018; Hukins, 2006; Rawn & Cross, 2008; Taatjes & Roth, 2005; Kreeger, 2001; Di Pietro et. al., 2002.
Animal subjects	Park et. al. 2019; Siegel et al. 2012; Xue et al. 2017; Park et. al.2019; Wang et al. 2013; Bootelho et. al, 2010; Robinson et. al, 2018; Xin et. al., 2018; Ghadami et. al., 2010; Bi et. al., 2017; Rollick et. al., 2018; De Moraes et. al., 2012; Mason et. al. 2017; Ghadami et. al., 2012; Bond et. al, 2019; Fu et. al., 2018; Peterson et. al., 2016; Kuyinu et. al., 2016; Munier et. al, 2016; Driessen et. al., 2014; Yasuo et. al., 2000; Kapila et. al., 2009; Fischer et. al., 2008; Wang et. al., 2009; Fischer et a.l, 2007; Abubaker et. al., 1996; Hashem et. al, 2006; Puri et. al., 2009; Eikermann-Haerter et. al., 2009; Ceccarelli et. al., 2003; Schütz et. al., 2009; D'Hooghe et. al., 2009; Watkin et. al., 2008.
No hormone levels	Lora et. al., 2016; Farzin et. al., 2018; Ribeiro-Dasilva et. al., 2017; Ungor et. al., 2014; LeResche et. al., 2013; Sherman et. al., 2005; Mayoral et. al., 2013; Turner et al., 2011; Wise et. al., 2000; Abubaker et. al., 1993

Not related to the question addressed	Sahu et al. 2019; Hajati et al. 2010; Bernier et al. 2011; Sahu et al. 2019; Wieckiewicz et al. 2014; Patil, 2013; Kumar et. al., 2017; Magri et. al., 2018; Turcio et. al., 2015; Sundström Poromaa et. al., 2019; Hajati et. al., 2010; Rezaii et. al., 2010; Aneja et. al., 2017; Gupta; Archarya, 2016; Cheng et. al., 2013; Devo & Leslie, 2013; Olama et. al., 2015; Kunimoto; Bajorath, 2017; Casarini et. al., 2018; Licausi et. al.,2013; Rodríguez-Razón et. al., 2018; Solzak et. al., 2017; Chasombat et. al., 2013; Brellenthin et. al., 2017; Ergün et. al., 2015; Hizjr et. al., 2017; Mihaljevic et. al., 2016; Wijaya et. al., 2017; Rebholz et. al., 2018; Peeraer et. al., 2015; Bathen et. al., 2013; Pasquier et. al., 2012; Maleki et. al, 2012; Nekora et. al., 2008; Watkin et. al., 2008; Penetar et. al., 2009; Lima et. al., 2019; Peräkylä et. al., 2009; Ahmed et. al., 2000; Reiman et. ao, 1996; Casarsa et. al., 2008; Mullins et. al., 2007; Cauwe et. al., 2007; Soydan et. al., 2014.

Source: Authors (2021).

The scoring questions were based on the "Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 Updated September 2006" (Higgins & Green, 2018), on the PRISMA 2009 checklist (Liberati et al. 2009), "Advice on how to write a systematic review. JM Wardlaw. 14th January 2010", and the quality assessment tool for diagnostic accuracy studies (QUADAS) recommended by Cochrane. The studies were scored according to the questions presented in Table 2. Each article was scored from 0 to 2 and the scores were added up. The methodology of each selected article was evaluated and the information included in the table. Scores from 0 to 8 were classified as a low evidence value, while scores from 9 to 11 and 12 to 14 were classified as a moderate and high evidence value respectively.

Table 2. Methodological evaluation of selected works.

QUESTIONS	METHODS	SCORING
Q1	Sample size	▪ 0-9 – **0 pts** ▪ 10-99 – **1 pt** ▪ >100 – **2 pts**
Q2	Control group	▪ none – **0 pts** ▪ present – **2 pts**
Q3	Inclusion criteria	▪ none – **0 pts** ▪ present, not restricted to one form of ▪ TMD – **1 pt** ▪ restricted to one form of TMD – **2 pts**
Q4	Exclusion criteria	▪ none – **0 pts** ▪ concomitant pain disorders OR other ▪ medications use OR systemic disease OR lactating OR pregnancy – **1 pt** ▪ concomitant pain disorders AND other ▪ medications use AND systemic disease AND lactating AND pregnancy – **2 pts**
Q5	Use of standardized examination protocol	▪ none – **0 pts** ▪ other protocols – **1pt** RDC/TMD – **2 pts**
Q6	Estrogen and Progesterone level assessment	▪ none – **0 pt** ▪ blood or saliva assessment not based on phases of ▪ the menstrual cycle – **1 pt** ▪ blood or saliva assessment based on phases of the menstrual cicle– **2 pts**
Q7	Conflict of interest	▪ present – **0 pts** ▪ no data – **1pt** ▪ none – **2 pts**

AUTHORS	TITLE	SCORING							TOTAL
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	
Patil *et al.* (2015)	Role of female reproductive hormones estrogen and progesterone in temporomandibular disorder in female patients	2	0	1	2	1	1	2	9
LeResche *et al.* (2005)	Musculoskeletal orofacial pain and other signs and symptoms of temporomandibular disorders during pregnancy: a prospective study.	1	2	1	0	2	1	2	9
Landi *et.al.* (2005)	Sexual hormone serum levels and temporomandibular disorders	1	2	1	0	2	2	2	10
Madani *et al.* (2013)	A cross-sectional study of the relationship between serum sexual hormone levels and internal derangement of temporomandibular joint.	2	2	2	2	2	2	2	14

;

3. Results

In general, few clinical trials have been developed comparing this relationship, although there are several reviews and studies in animals addressing the topic. Analyzing this smaller amount, heterogeneity is perceived in relation to the method of diagnosis of the disease, as well as the complementary exam and the phase to be performed the hormonal count.

Regarding diagnosis among patients, only one study (Patil *et al.*, 2015) did not use the RDC / TMD (Diagnostic Criteria for Research on Temporomandibular Dysfunction) as a method, addressing the anamnesis questionnaire proposed by Fonseca et al. 1994. The analysis of hormone levels was performed mainly through blood collection, except for one case (LeResche *et al.*, 2005) where the entire unstimulated saliva was collected for this purpose, as shown in Table 3 below.

Table 3. Objectives and methods of the studies.

STUDY	TITLE	AIM AND METHOD OF THE STUDY
Patil *et al.* (2015)	Role of female reproductive hormones estrogen and progesterone in temporomandibular disorder in female patients.	▪ **Aim of study:** The aim of the present study is to investigate the role of female reproductive hormones estrogen and progesterone in temporomandibular disorder (TMD) in female patients. ▪ **Compared variables:** Estrogen and Progesterone levels. ▪ **TMD diagnosis method:** Questionnaire proposed by Fonseca ▪ **Hormone level assessment:** Blood sample
Madani *et al.* (2013)	A cross-sectional study of the relationship between serum sexual hormone levels and internal derangement of temporomandibular joint.	▪ **Aim of study:** The aim of this study was to evaluate 17b-oestradiol and progesterone serum levels in menstruating women affected by internal derangement of the TMJ. ▪ **Compared variables:** Estrogen and Progesterone levels. ▪ **TMD diagnosis method:** Clinical examination according to RDC/TMD ▪ **Hormone level assessment:** Blood sample
Landi *et al.* (2005)	Sexual hormone serum levels and temporomandibular disorders. A preliminary study.	▪ **Aim of study:** The aim of the present study was to investigate the role of sexual hormones in a young adult population affected by articular forms of temporomandibular disorders (TMD), measuring 17b-estradiol and progesterone serum levels. ▪ **Compared variables:** Estrogen and Progesterone levels. ▪ **TMD diagnosis method:** Clinical examination according to RDC/TMD ▪ **Hormone level assessment:** Blood sample
LeResche *et al.* (2005)	Musculoskeletal orofacial pain and other signs and symptoms of temporomandibular disorders during pregnancy: a prospective study.	▪ **Aim of study:** To describe the course of reported musculoskeletal pain in the temporomandibular region and other signs and symptoms of temporomandibular disorders (TMD) as well as psychological distress over the course of pregnancy and one year postpartum. ▪ **Compared variables:** Musculoskeletal pain in the temporomandibular region Estrogen levels (measured in the 3rd, 6th and 9th month of pregnancy and one year postpartum) Pain severity (the Graded Chronic Pain Scale) ▪ **TMD diagnosis method:** Clinical examination according to RDC/TMD ▪ **Hormone level assessment:** Unstimulated saliva samples

Source: Authors.

The relationship between estrogen levels was observed in three studies (Patil *et al.*, 2015; Landi *et al.*, 2005; LeResche *et al.*, 2005), while another study (Madani *et al.*, 2013) did not showed altering estrogen levels in women who had crackles when compared to the control group. The association of progesterone has also been found in three studies (Patil *et al.*, 2015; Madani *et al.*, 2013; LeResche *et al.*, 2005). One (Landi *et al.*, 2005) of them found no variation in serum progesterone levels, as shown in Table 4.

Table 4. Characteristics of the included studies and analysis of the relationship between hormonal levels.

STUDY	DESING	N	AGE	HORMONAL LEVELS		RELATIONSHIP WITH TMD	
				ESTROGEN (E)	PROGESTERONE (P)	E	P
Patil *et. al.* (2015)	Case-control study	200	14-40 years (mean ± standard deviation = 24 ± 8)	Severe cases: 444,2 ± 3,57pg/mL Moderate cases: 264,5± 2,23pg/mL Mild cases: 199,8 ± 3,46pg/mL	Severe cases: 1,88 ± 41,9ng/mL Moderate cases: 1,64 ± 33,2ng/mL Mild cases: 1,52 ± 34,7ng/mL	YES	YES
Madani *et. al*. (2013)	Cross-sectional study	TMD group: 47 Control group: 95	TMD group: 28.5 ± 5.4 Control group: 31.0 ± 7.2	TMD group: 164 ± 104.6 pg/mL^{-1} (mean ± s.d) Group control: 162 ± 129.9pg/mL^{-1}	TMD group: 8,4 ± 6,8ng/mL^{-1} Group control: 11,6 ± 10,4ng/mL^{-1}	NO	YES
Landi *et. al.* (2005)	Case-control study	TMD group: 40 (20 women + 20 men) Control group: 32 (16 women + 16 men)	TMD group: Women: 25,6 ± 4,1; Men: 24,8 ± 3,1 Control group: Women: 22,3 ± 1,5; Men: 24,4 ± 2,3	Follicular Phase TMD group (woman): 112,0 + 42,6pg/mL Group Control (woman): 139,0 + 18,4pg/mL Luteal Phase: TMD group (woman): 203,0 + 71,1pg/mL Group Control (woman): 110,6 + 44,2pg/mL	Follicular Phase TMD group (woman): 1,08 + 0,30ng/mL Group Control (woman): 0,97 + 0,25ng/mL Luteal Phase: TMD group (woman): 14,10 + 3,70pg/mL Group Control (woman): 10,90 + 1,10ng/mL	YES	NO
LeResche *et. al*. (2005)	Prospective cohort study	TMD group: 19 (pregnant women)	Study group: 28.5 ± 4.9 Control	3-Month (Both groups): 6 pmol/L to 72 pmol/L; 6 TO 9-Month (Both	3-Month (Both groups): 201 pmol/L to 1,812pmol/L; 6 TO 9-Month (Both groups): mean 535pmol/L	YES	YES

		Control group: 16 (pregnant women)	group: 28.4 ± 4.1	groups): mean 21pmol/L to 134 pmol/L; Postpartum: 1.8pmol/L	to 1.826pmol/L; Postpartum:67pmol/L		

Source: Authors.

Regarding the classification of evidence, analyzing the questions and the questions scores found in Table 2, it is possible to classify most studies (Patil *et al.*, 2015; Landi *et al.*, 2005; LeResche *et al.*, 2005) with moderate value, while one with high value (Madani *et al.*, 2013). However, the lack of alignment between studies makes it difficult to associate the variations present in the configurations as in the hormonal processes.

It was not possible to state through the selected researches whether changes in the levels of progesterone and estrogen can predispose women to the development of the disease or be related to the severity of existing cases; but that there is a great possibility in this relationship.

4. Discussion

Examining the multifactorial character of Temporomandibular Dysfunction and its broad clinical picture of signs and symptoms, several criteria make its diagnosis possible. The RDC / TMD, used by most selected studies (Landi *et al.*, 2005; Madani *et al.*, 2013; LeResche *et al.*, 2005), is one of the diagnostic classifications available in the broadest literature and accepted in clinical research, with acceptable levels of reliability to assess the standardized form up to clinical subtypes - myogenic and atherogenic - from the disease (Chaves, Oliveira & Grossi, 2008). The Fonseca Questionnaire and Anamnesis Index (Fonseca *et al.*, 1994), used in one of the studies (Patil *et al.*, 2015), is indicated to evaluate mainly the severity of symptomatic conditions, being indicated for population epidemiological studies due to its ease of application, not being very usual for trials clinical, considering that it does not offer diagnostic classification (Chaves, Oliveira & Grossi, 2008).

Serum hormone levels were measured by collecting blood (Patil *et al.*, 2015; Landi *et al.*, 2005; Madani *et al.*, 2013) and saliva (LeResche *et al.*, 2005). Saliva can be presented as a simplified and non-invasive source for the collection of samples for hormonal analysis and, although not yet clinically reliable, it has been widely used to assess the concentration of steroids, polypeptides, antibodies, alcohol, and drugs illicit use (Puhakkra & Peltola, 2020). Its use in substitution to the traditional method of laboratory analysis presents as a limitation the difficulty of detecting some proteins that present themselves in low concentration in the salivary fluid (Rilling *et al.*, 1996; Ghiciuc *et al.*, 2016).

The distribution of age and gender in cases of orofacial pain suggests a possible association between its pathogenesis and estrogen (Ghiciuc *et al.*, 2016). Evidence shows that its levels are not only related to pain modulation but the development and restitution of the TMJ and associated structures. Besides, it can influence the synthesis of collagen and elastin, which make up the articular disc (Gupta *et al*., 2011 Fenzi & Rizzuto, 2001; Tashiro, Okamoto & Bereiter, 2011).

Among the studies reviewed, the only one did not describe a relationship between estrogen and TMD (Madani *et al.*, 2013). In it, women in the menstrual period with disorders in the temporomandibular joint were evaluated regarding the crackling resulting from the wear of the articular disc where there was no significant difference between the control group and those with values below or above normal. This result differs from the other studies reviewed (Patil *et al.*, 2015; Landi *et al.*, 2005; LeResche *et al.*, 2005) and also from studies carried out in animals, in which the TMJ of ovariectomized and non-

ovariectomized rats with and without hormonal supplementation was evaluated, demonstrating that estrogen in physiological concentration plays a role in joint remodeling (Yasuoka *et al.*, 2000). Other studies (Kamiya *et al*., 2013; Abdrabuh & Balion, 2020; Kou *et al*., 2011) with similar methodology also reported that the deficiency of this hormone caused degradation of the articular disc and the cartilaginous layer of the mandibular condyle in their samples.

The possible relationship between progesterone and TMD cases occurred when observing that pregnant women have fewer symptoms than non-pregnant women (LeResche *et al.*, 2005). This hormone is involved in the modulation of inflammatory processes and is overexpressed during pregnancy (Xue *et al.*, 2017). Three reviewed papers analyzed and confirmed that serum progesterone variations are related to the inflammatory severity of TMD (Patil *et al*., 2015; Madani *et al.*, 2013; LeResche *et al.*, 2005).

Animal studies (Hormung *et al.*, 2020; Kou *et al*., 2011) show that progesterone can offer continuous relief in orofacial pain and that, in cases of reduced levels, an increase in the inflammatory process was triggered; while its maintenance at normal rates shows a reduction in edema and pain. Also, a systematic review (Berger *et al*., 2015) that analyzed only the relationship of estrogen points not only to the deficiency and limitations of the studies selected in its selection but also to inconsistency between its results, and even though there is stagnation in this area of knowledge, even there is still no precise thing about the relationship. These data corroborate those that were addressed, however, in this review we also take into account the role of progesterone shown in research.

5. Conclusion

The studies developed that addressed the possible relationship between estrogen and progesterone with the highest incidence of Temporomandibular Disorder in women present divergences between them, ranging from the experimental design to the same result. Therefore, it is not possible to clarify whether there is, in fact, a relationship between hormonal variation and the greater female predisposition to the development and severity of the disease. However, even with the strong evidence produced by them, this review suggests the realization of new clinical trials that separate the different hormonal fluctuations that range from reproductive age to post-menopause so that a survey with methodological quality studies is possible.

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