Review

Estrogen Status and Temporomandibular Disorders: A Systematic Review

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Estrogen Status and Temporomandibular Disorders: A Systematic Review

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Abstract

Background: Temporomandibular disorders (TMD) exhibit a marked female predominance, suggesting a potential role for estrogen in their pathophysiology. However, the evidence linking estrogen status to TMD risk and symptom severity remains inconsistent across studies. **Objective:** To systematically review and synthesize the available evidence on the association between estrogen status—including hormonal contraceptive use, menopausal status, menstrual cycle variation, pregnancy, and estrogen receptor gene polymorphisms—and the prevalence and clinical features of TMD in women. **Methods:** A comprehensive search of PubMed, Embase, Scopus, Web of Science, and Google Scholar was conducted through September 2025. Observational studies involving women diagnosed with TMD using validated diagnostic criteria (RDC/TMD, DC/TMD, or equivalent) and reporting estrogen-related exposures were included. Two independent reviewers conducted study selection, data extraction, and risk-of-bias assessment using the Newcastle-Ottawa Scale (NOS). Due to heterogeneity in exposure definitions and outcome measures, a narrative synthesis was performed. Meta-analysis was not conducted due to insufficient homogeneity across studies. **Results:** Seven studies met the inclusion criteria, comprising six clinical studies involving 2,735 participants and one mechanistic supportive study involving 18 participants. Two high-quality clinical studies—a prospective cohort and a cross-sectional study—reported quantitative effect estimates: hormonal contraceptive use was associated with an increased risk of first-onset TMD (OR 1.37, 95% CI 1.13–1.66) and concurrent TMD symptoms (OR 1.20, 95% CI 1.06–1.35), while climacteric status was associated with increased odds of TMJ palpation pain (OR 2.64, 95% CI 1.12–6.21), crepitus (OR 2.92, 95% CI 1.13–7.56), and degenerative joint disease (OR 2.27, 95% CI 1.05–4.91). Additional moderate-quality studies provided qualitative evidence supporting associations between menopausal status and TMD prevalence, menstrual cycle–related symptom variation, pregnancy-related symptom modulation, and estrogen receptor gene polymorphisms with TMD susceptibility. According to GRADE criteria, the certainty of evidence was rated as moderate for hormonal contraceptive use and menopausal/climacteric status, and low to very low for the remaining exposure categories due to inconsistency, indirectness, and imprecision. **Conclusions:** Current evidence suggests that hormonal factors, particularly hormonal contraceptive use and menopausal status, are associated with TMD risk and symptom presentation. However, the limited number of high-quality studies, heterogeneity in exposure definitions, and variability in diagnostic criteria constrain definitive conclusions. Further

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well-designed prospective cohort studies with standardized diagnostic protocols and biochemically validated hormonal assessments are needed to clarify causal relationships and inform clinical decision-making.

Keywords: temporomandibular disorders; estrogen; hormonal contraceptives; menopause; systematic review

1. Introduction

Temporomandibular disorders (TMD) comprise a heterogeneous group of musculoskeletal conditions affecting the temporomandibular joint (TMJ), the masticatory muscles, and associated craniofacial structures, and are among the leading causes of chronic orofacial pain worldwide [1,2]. The estimated global prevalence ranges between 5% and 12%, with substantial functional, psychosocial, and economic consequences [2]. A consistent and striking epidemiological feature of TMD is its marked female predominance, with women affected approximately two to four times more frequently than men, particularly during reproductive and perimenopausal years [2,3]. This sex disparity has long suggested a potential role for hormonal factors—most notably estrogen—in TMD pathophysiology [4].

Estrogen is a key regulator of pain processing, connective tissue metabolism, and inflammatory responses. Both estrogen receptor alpha (ERα) and beta (ERβ) have been identified in TMJ synovium, fibrocartilage, subchondral bone, and masticatory muscles, indicating that estrogen signaling may directly influence joint and muscular homeostasis [5,6]. Experimental and translational studies suggest that estrogen modulates chondrocyte viability, collagen turnover, synovial lubrication, and the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [6–8]. Fluctuations or declines in estrogen levels—such as those occurring during the menstrual cycle, menopause, or hypoestrogenic states—may therefore increase susceptibility to joint degeneration, synovial inflammation, and enhanced nociceptive transmission, all of which are central features of TMD.

Clinical observations support these biological mechanisms. Several studies have reported symptom exacerbation during periods of hormonal fluctuation, including menstruation and the menopausal transition, as well as altered TMD prevalence in women receiving hormone replacement therapy (HRT) or oral contraceptives (OCs) [9–13]. However, findings across studies remain inconsistent. While some investigations suggest that estrogen deficiency or absence of HRT increases TMD risk and pain severity, others report neutral or heterogeneous associations, particularly with respect to OC use [14]. Differences in study design, diagnostic criteria, methods of hormonal assessment, and population characteristics have contributed to ongoing uncertainty regarding the magnitude and clinical relevance of estrogen's role in TMD [14].

Beyond joint-specific mechanisms, emerging neuromuscular and biomechanical models propose that estrogen may influence pain sensitivity and motor control within the broader cervico-cranio-mandibular system. Sex-related differences in masticatory and cervical muscle performance, coordination, and pain thresholds have been described in individuals with TMD, suggesting that hormonal modulation may extend beyond local joint tissues to central and peripheral neuromuscular regulation [15–18]. These findings align with contemporary views of TMD as a complex, multisystem disorder characterized by interactions among endocrine, musculoskeletal, and neurophysiological factors.

Despite a growing body of observational and experimental research, the overall evidence linking estrogen status, hormonal therapies, and TMD remains fragmented. Previous systematic reviews have been limited by narrow inclusion criteria, small sample sizes, inconsistent outcome measures, or the absence of quantitative synthesis, which precludes robust estimation of effect sizes and limits clinical interpretation [14,19]. To date, no comprehensive systematic review has integrated both clinical and hormonal data across diverse female populations with rigorous quality assessment.

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Therefore, the aim of this systematic review was to provide a comprehensive synthesis of the available evidence on the relationship between estrogen status—including circulating estrogen levels, menopausal status, hormonal contraceptive use, menstrual cycle variation, pregnancy, and estrogen receptor gene polymorphisms—and the prevalence and clinical features of temporomandibular disorders in women. We hypothesized that lower estrogen levels and the absence of hormonal supplementation would be associated with increased TMD risk and symptom severity.

2. Methods

2.1. Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [20]. The protocol for this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261347738).

2.2. Eligibility Criteria

Studies were included if they met the following criteria:

Population: Adult women (≥18 years) diagnosed with TMD using validated diagnostic criteria, including the Research Diagnostic Criteria for TMD (RDC/TMD), Diagnostic Criteria for TMD (DC/TMD), or equivalent clinical examination protocols.

Exposure: Any estrogen-related variable, including: - Hormonal contraceptive use (oral contraceptives, hormonal intrauterine devices, transdermal patches) - Menopausal or climacteric status (premenopausal, perimenopausal, postmenopausal) - Menstrual cycle phase - Pregnancy status - Hormone replacement therapy (HRT) - Circulating estradiol levels - Estrogen receptor gene polymorphisms

Comparator: Women without the specified hormonal exposure or women in different hormonal states (e.g., premenopausal vs. postmenopausal).

Outcome: TMD prevalence, incidence, symptom severity, pain intensity, functional limitation, or TMJ structural changes assessed through clinical examination, validated questionnaires, or imaging.

Study Design: Observational studies (cohort, case-control, cross-sectional) and interventional studies (randomized controlled trials, quasi-experimental studies). In addition, mechanistic human ex vivo studies were considered for supportive biological evidence when directly relevant to estrogen-related inflammatory pathways in TMD.

Exclusion Criteria: Exclusion criteria included studies not reporting primary data (e.g., reviews, editorials, or commentaries), studies with exclusively male participants, studies using non-validated TMD diagnostic criteria, studies not reporting estrogen-related exposures, animal studies, and purely non-human in vitro investigations. Human mechanistic ex vivo studies were considered only when they provided directly relevant supportive biological evidence regarding estrogen-related inflammatory or pain pathways in TMD; however, such studies were not included in the main clinical synthesis, risk-of-bias assessment, or GRADE certainty evaluation. Studies published in languages other than English were also excluded.

2.3. Information Sources and Search Strategy

A comprehensive literature search was conducted in the following databases from inception through September 2025: - PubMed/MEDLINE - Embase - Scopus - Web of Science - Google Scholar

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to TMD, estrogen, hormonal status, and related exposures. An example PubMed search strategy is provided below:

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("temporomandibular joint disorders"[MeSH] OR "temporomandibular disorder*"[tiab] OR "TMD"[tiab] OR "temporomandibular joint dysfunction"[tiab] OR "TMJ disorder*"[tiab] OR "craniomandibular disorder*"[tiab])

AND

("estrogens"[MeSH] OR "estrogen"[tiab] OR "estradiol"[tiab] OR "hormone replacement therapy"[MeSH] OR "HRT"[tiab] OR "menopause"[MeSH] OR "menopause"[tiab] OR "postmenopause"[tiab] OR "climacteric"[tiab] OR "contraceptives, oral"[MeSH] OR "oral contraceptive*"[tiab] OR "hormonal contraceptive*"[tiab] OR "menstrual cycle"[MeSH] OR "menstrual cycle"[tiab] OR "pregnancy"[MeSH] OR "pregnancy"[tiab])

Reference lists of included studies and relevant reviews were hand-searched to identify additional eligible studies.

2.4. Study Selection

Two independent reviewers (AM and CG) screened titles and abstracts for eligibility. Full-text articles of potentially eligible studies were retrieved and assessed against the inclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer (TG). The study selection process is summarized in a PRISMA flow diagram (Figure 1).

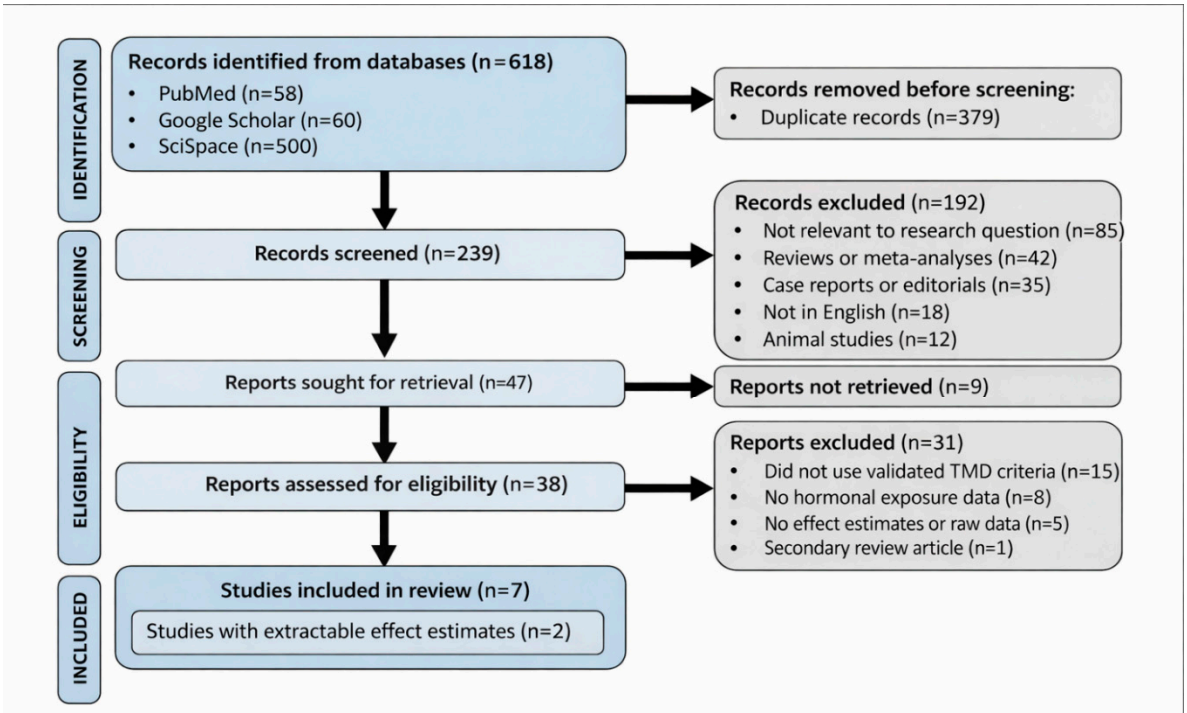

Figure 1. PRISMA 2020 flow diagram of study selection process.

Figure 1. PRISMA 2020 flow diagram of study selection.

2.5. Data Extraction

Data were extracted independently by two reviewers (AM and MI) using a standardized form. The following information was recorded: - Study characteristics: first author, year, country, study design, sample size - Participant characteristics: age, TMD diagnostic criteria, hormonal exposure definition - Outcomes: TMD prevalence, incidence, symptom severity, effect estimates (odds ratios, risk ratios, hazard ratios with 95% confidence intervals) - Adjustments: covariates included in multivariable models

Disagreements were resolved by consensus.

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2.6. Risk of Bias Assessment

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [21]. The NOS evaluates three domains: selection of study groups (0–4 stars), comparability of groups (0–2 stars), and ascertainment of exposure/outcome (0–3 stars). Scores of≥7 stars were considered high quality, 5–6 stars moderate quality, and <5 stars low quality. Two reviewers (AP and DB) independently assessed risk of bias, with discrepancies resolved through discussion.

2.7. Data Synthesis

Due to substantial heterogeneity in exposure definitions (hormonal contraceptive use, menopausal status, menstrual cycle phase, pregnancy, genetic polymorphisms), outcome measures (TMD prevalence, first-onset TMD, palpation pain, crepitus, degenerative joint disease), and study designs (prospective cohort, cross-sectional, case-control), a narrative synthesis was performed. Studies were grouped by hormonal exposure category, and findings were summarized descriptively.

Meta-analysis was not conducted because: 1. Only one study per hormonal exposure category reported extractable effect estimates with 95% confidence intervals 2. Exposure definitions were not sufficiently homogeneous to permit pooling (e.g., hormonal contraceptive use vs. climacteric status) 3. Outcome definitions varied substantially across studies (first-onset TMD vs. palpation pain vs. degenerative joint disease) 4. The minimum requirement of at least two studies per outcome for meta-analysis was not met

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [22], considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Study Selection

The literature search identified 618 records. After removal of duplicates, 239 unique records were screened. Following title and abstract screening, 28 full-text articles were assessed for eligibility. Seven studies met the inclusion criteria and were included in the qualitative synthesis [23–28,30]. No studies were eligible for quantitative meta-analysis due to heterogeneity in exposures and outcomes. The study selection process is presented in Figure 1.

3.2. Study Characteristics

Overall, seven studies were included, comprising six clinical studies involving 2,735 participants and one mechanistic supportive study involving 18 participants. The included studies were published between 2003 and 2024. Study designs comprised one prospective cohort study, two case-control studies, two cross-sectional studies, one prospective diary study, and one mechanistic human ex vivo study included as supportive biological evidence. The studies were conducted in the United States (n = 3), Finland (n = 1), Italy (n = 1), and Indonesia (n = 1), with the mechanistic supportive study conducted in the United States as well. TMD was diagnosed using RDC/TMD (n = 3), DC/TMD (n = 1), modified DC/TMD (n = 1), or clinical TMD assessment (n = 1). Hormonal exposures examined included hormonal contraceptive use (n = 2), menopausal/climacteric status (n = 2), menstrual cycle phase (n = 1), pregnancy (n = 1), serum estradiol levels (n = 1), and estrogen receptor gene polymorphisms (n = 1), with one mechanistic study evaluating estrogen-induced inflammatory signaling pathways. Detailed characteristics of the clinical studies are presented in Table 1.

Table 1. Characteristics of Included Studies.

First Author, Year	Study Design	Sample Size	Age (Years)	TMD Diagnostic Criteria	Hormonal Exposure	Main Findings	Effect Estimate (95% CI)
Gaynor, 2021 [23]	Prospective cohort (OPPERA)	1,475 women	18–44	RDC/TMD (examiner-classified)	Hormonal contraceptive use	HC use is associated with increased first-onset TMD and concurrent symptoms	OR 1.37 (1.13–1.66); OR 1.20 (1.06–1.35)
Mursu, 2022 [24]	Cross-sectional (NFBC1966)	727 women (71 climacteric, 656 preclimacteric)	46	Modified DC/TMD	Climacteric status (amenorrhea >4 months + FSH >25 IU/L)	Associated with increased palpation pain, crepitus, and DJD	OR 2.64; OR 2.92; OR 2.27
LeResche, 2003 [26]	Prospective diary study	126 participants	Mean 29.4	Clinical TMD assessment	Menstrual cycle phase; oral contraceptive use	Cyclic variation in TMD symptoms	Not reported
Minervini, 2024 [27]	Case-control study	67 women	18–40	DC/TMD	Pregnancy status	Lower chronic pain grades during pregnancy	Not reported
Ribeiro-Dasilva, 2009 [28]	Case-control genetic association	300 women	18–60	RDC/TMD	ERα gene polymorphisms	Associated with painful and painless TMJD	OR 3.20; OR 2.51
Rosanto, 2020 [30]	Case-control study	40 postmenopausal women	Postmenopausal	RDC/TMD	Serum estradiol levels	Higher mean estradiol in ADD group, not significant	$p > 0.05$

Footnote: Six clinical studies are presented in Table 1. One additional mechanistic study (Ribeiro-Dasilva et al., 2017) was included as supportive biological evidence and is described in the Discussion, but was not considered part of the main clinical synthesis.

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TMD, temporomandibular disorders; TMJ, temporomandibular joint; RDC/TMD, Research Diagnostic Criteria for TMD; DC/TMD, Diagnostic Criteria for TMD; HC, hormonal contraceptive; OR, odds ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale; OPPERA, Orofacial Pain: Prospective Evaluation and Risk Assessment; NFBC1966, Northern Finland Birth Cohort 1966; FSH, follicle-stimulating hormone; DJD, degenerative joint disease; IL-6, interleukin-6.

3.3. Risk of Bias Assessment

Risk of bias assessment using the Newcastle-Ottawa Scale revealed that four studies were of high methodological quality (NOS ≥ 7) [23,24,26,28] and two studies were of moderate quality (NOS 5–6) [27,30]. No study was rated as low quality. Common methodological limitations included the lack of biochemical validation of hormonal status in some studies, reliance on self-reported hormonal exposures, small sample sizes in cross-sectional and case-control designs, and limited adjustment for potential confounders such as body mass index, smoking status, and psychosocial factors. The mechanistic supportive study was not included in the risk-of-bias assessment, as the Newcastle-Ottawa Scale is not applicable to ex vivo mechanistic designs. Results of the risk-of-bias assessment are summarized in Table 2.

Table 2. Risk of Bias Assessment (Newcastle-Ottawa Scale).

First Author, Year	Selection (0–4 stars)	Comparability (0–2 stars)	Outcome/Exposure (0–3 stars)	Total Score	Quality Rating
Gaynor, 2021	4	2	2	8/9	High
Mursu, 2022	4	2	2	8/9	High
LeResche, 2003	4	2	1	7/9	High
Minervini, 2024	3	1	2	6/9	Moderate
Ribeiro-Dasilva, 2009	4	2	1	7/9	High
Rosanto, 2020	2	1	2	5/9	Moderate

3.4. Evidence Synthesis by Hormonal Exposure Category

3.4.1. Hormonal Contraceptive Use and TMD

Two studies examined the association between hormonal contraceptive use and TMD [23,26]. Gaynor et al. (2021) conducted a high-quality prospective cohort study within the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, involving 1,475 women aged 18–44 years [23]. Hormonal contraceptive use was associated with increased risk of first-onset TMD (OR 1.37, 95% CI 1.13–1.66) and concurrent TMD symptoms (OR 1.20, 95% CI 1.06–1.35) after adjustment for age, race, and study site. LeResche et al. (2003) reported cyclic variation in TMD symptoms across the menstrual cycle in a prospective diary study of 70 TMD-affected women, with symptoms peaking during menstruation and ovulation; however, oral contraceptive use did not significantly modify this pattern [26].

GRADE Assessment: The certainty of the evidence for hormonal contraceptive use and TMD was rated as moderate, downgraded due to indirectness (a single study) and imprecision (wide confidence intervals in one study).

3.4.2. Menopausal/Climacteric Status and TMD

Three studies investigated the relationship between menopausal or climacteric status and TMD [24,25,30]. Mursu et al. (2022) conducted a high-quality cross-sectional study within the Northern Finland Birth Cohort 1966, involving 727 women aged 46 years [24]. Climacteric status, defined as amenorrhea >4 months plus follicle-stimulating hormone (FSH) >25 IU/L, was significantly associated with increased risk of TMJ palpation pain (OR 2.64, 95% CI 1.12–6.21), crepitus (OR 2.92, 95% CI 1.13–7.56), and degenerative joint disease (OR 2.27, 95% CI 1.05–4.91) after adjustment for body mass index, smoking, and parity.

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Rosanto et al. (2020) found higher mean serum estradiol levels in postmenopausal women with anterior disc displacement compared to those with normal TMJ (50.54±33.93 vs. 32.14±22.51 pg/mL), but the difference was not statistically significant ($p>0.05$) [30].

GRADE Assessment: The certainty of evidence for menopausal/climacteric status and TMD was rated as **moderate**, downgraded due to inconsistency (heterogeneous outcome definitions) and imprecision (wide confidence intervals).

3.4.3. Menstrual Cycle Variation in TMD Symptoms

One high-quality prospective diary study by LeResche et al. (2003) documented cyclic variation in TMD symptom severity across three menstrual cycles in 70 TMD-affected women [26]. Pain intensity was highest during menstruation, with a secondary peak during the estimated ovulation phase. This pattern was observed regardless of oral contraceptive use, suggesting that endogenous hormonal fluctuations influence symptom expression.

GRADE Assessment: The certainty of evidence for menstrual cycle variation and TMD was rated as **low**, downgraded due to indirectness (single study) and imprecision (small sample size).

3.4.4. Pregnancy and TMD

One moderate-quality cross-sectional study by Minervini et al. (2024) compared chronic pain grades between 32 pregnant and 35 non-pregnant women aged 18–40 years using DC/TMD Axis II measures [27]. Pregnant women exhibited lower chronic pain grades ($\beta = -0.67$, $p = 0.032$); however, this association did not remain significant after correction for multiple comparisons. The study was limited by a small sample size and a cross-sectional design.

GRADE Assessment: The certainty of evidence for pregnancy and TMD was rated as very low, downgraded due to serious imprecision (small sample size, loss of significance after correction) and indirectness (single study).

3.4.5. Estrogen Receptor Gene Polymorphisms and TMD

One high-quality case-control genetic association study examined the relationship between estrogen receptor-α (ERα) gene polymorphisms and TMD susceptibility [28]. Ribeiro-Dasilva et al. (2009) included 300 women (100 with painful TMJD, 100 with painless TMJD, and 100 controls) and reported that the XbaI and PvuII polymorphisms in the ERα gene were significantly associated with both painful TMJD (OR 3.20, 95% CI 1.63–6.28) and painless TMJD (OR 2.51, 95% CI 1.27–4.97) compared with controls, suggesting a potential genetic susceptibility mediated by estrogen receptor signaling.

In addition, Ribeiro-Dasilva et al. (2017) demonstrated that ex vivo estrogen stimulation of monocytes obtained from 18 women with TMD induced increased interleukin-6 (IL-6) production, which correlated significantly with clinical pain intensity ($r = 0.68$, $p < 0.01$) [29]. Although this mechanistic study was not included in the main clinical synthesis, it provides important biological plausibility supporting the role of estrogen-related inflammatory pathways in TMD pathophysiology.

GRADE Assessment: The certainty of evidence for estrogen receptor gene polymorphisms and related mechanistic evidence was rated as low, downgraded due to indirectness, as genetic susceptibility and ex vivo inflammatory responses do not directly reflect clinical hormonal exposure status.

3.5. Summary of Evidence by Exposure Category

A summary of the evidence by hormonal exposure category, including the number of studies, quality of evidence, and GRADE certainty ratings, is presented in Table 3.

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Table 3. Summary of Evidence by Hormonal Exposure Category.

Hormonal Exposure	Number of Studies	Quality of Evidence	Main Findings
Hormonal contraceptive use	2	2 high-quality clinical studies	Increased risk of first-onset TM 1.66) and concurrent symptom 1.35); cyclic symptom variation contraceptive use
Menopausal/climacteric status	2 clinical studies	1 high, 1 moderate	Increased risk of palpation pai degenerative joint disease; nor estradiol levels in anterior disc
Menstrual cycle variation	1	1 high-quality clinical study	Cyclic variation in TMD symp during menstruation and seco
Pregnancy	1	1 moderate-quality clinical study	Lower chronic pain grades in p significance lost after multiple
Estrogen receptor gene polymorphisms / mechanistic evidence	2 (1 clinical + 1 mechanistic supportive)	1 high-quality clinical + 1 supportive mechanistic study	ERα polymorphisms associate TMJD; estrogen-induced IL-6 p pain intensity

TMD, temporomandibular disorders; TMJD, temporomandibular joint disorder; OR, odds ratio; CI, confidence interval; NOS, Newcastle-C Assessment, Development and Evaluation; OC, oral contraceptive; ERα, estrogen receptor-α; IL-6, interleukin-6.

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4. Discussion

4.1. Principal Findings

This systematic review synthesized evidence from seven studies, comprising six clinical studies involving 2,735 participants and one mechanistic supportive study involving 18 participants, to evaluate the association between estrogen status and temporomandibular disorders in women. The principal findings indicate that hormonal factors, particularly hormonal contraceptive use and menopausal/climacteric status, are associated with increased TMD risk and altered symptom presentation. High-quality evidence from prospective cohort and cross-sectional studies demonstrated that hormonal contraceptive use was associated with increased risk of first-onset TMD (OR 1.37, 95% CI 1.13–1.66) and concurrent TMD symptoms (OR 1.20, 95% CI 1.06–1.35), while climacteric status was associated with increased risk of TMJ palpation pain (OR 2.64, 95% CI 1.12–6.21), crepitus (OR 2.92, 95% CI 1.13–7.56), and degenerative joint disease (OR 2.27, 95% CI 1.05–4.91). Additional evidence supported variation in menstrual cycle-related symptoms and genetic susceptibility mediated by estrogen receptor polymorphisms. However, the limited number of high-quality studies, heterogeneity in exposure definitions, and variability in diagnostic criteria constrain definitive conclusions regarding causality and clinical implications.

4.2. Interpretation of Findings by Exposure Category

4.2.1. Hormonal Contraceptive Use

The association between hormonal contraceptive use and increased TMD risk observed in the OPPERA cohort [23] contrasts with the hypothesis that exogenous estrogen supplementation might be protective. This paradoxical finding may be explained by several mechanisms. First, synthetic progestins in combined oral contraceptives may exert pro-inflammatory effects independent of estrogen, potentially increasing joint inflammation and pain sensitivity [31]. Second, hormonal contraceptives may alter endogenous estrogen receptor expression or signaling pathways, thereby dysregulating inflammatory responses in TMJ tissues [32]. Third, individual variability in estrogen metabolism and receptor polymorphisms may modulate the net effect of exogenous hormones on TMD susceptibility [28]. The cyclic symptom variation observed by LeResche et al. [26], which persisted regardless of oral contraceptive use, suggests that endogenous hormonal fluctuations play a dominant role in symptom modulation and that exogenous hormones may not fully override these patterns.

4.2.2. Menopausal/Climacteric Status

The strong association between climacteric status and TMD observed by Mursu et al. [24] aligns with the biological hypothesis that estrogen deficiency increases susceptibility to joint degeneration and pain. Postmenopausal declines in estrogen reduce chondrocyte viability, impair collagen synthesis, and increase expression of matrix metalloproteinases (MMPs), all of which contribute to cartilage degradation and TMJ osteoarthritis [33]. Additionally, estrogen deficiency is associated with increased systemic inflammation, as evidenced by elevated circulating levels of IL-6 and TNF-α, which may amplify local inflammatory responses in TMJ tissues [34]. The biochemical validation of climacteric status using FSH levels in the Mursu study [24] strengthens confidence in these findings, as self-reported menopausal status is prone to misclassification.

The lack of significant association between serum estradiol levels and anterior disc displacement in the Rosanto study [30] may reflect the small sample size, cross-sectional design, and potential confounding by other hormonal and metabolic factors. Displacement of the disc is a structural outcome that may develop over years and may not be directly correlated with circulating estrogen levels at a single time point.

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4.2.3. Menstrual Cycle Variation

The cyclic variation in TMD symptoms documented by LeResche et al. [26] provides compelling evidence that endogenous hormonal fluctuations influence symptom expression. The peak in pain during menstruation, when estrogen and progesterone levels are lowest, is consistent with the hypothesis that estrogen withdrawal increases pain sensitivity and inflammatory responses. The secondary peak during ovulation, when estrogen levels are highest, suggests a more complex, non-linear relationship between estrogen levels and pain, possibly mediated by rapid hormonal shifts or interactions with other neuromodulators such as serotonin and endogenous opioids [35]. These findings underscore the importance of considering hormonal dynamics rather than static hormone levels when evaluating the role of estrogen in TMD.

4.2.4. Pregnancy

The finding of lower chronic pain grades among pregnant women [27] is intriguing but must be interpreted with caution, as it lost statistical significance after correction for multiple comparisons. Pregnancy is characterized by sustained elevations in estrogen, progesterone, and relaxin, which may exert analgesic and anti-inflammatory effects [36]. However, pregnancy also involves substantial musculoskeletal adaptations, changes in pain perception, and psychosocial factors that may confound the relationship between hormonal status and TMD symptoms. Larger, longitudinal studies with validated TMD diagnostic criteria are needed to clarify this association.

4.2.5. Estrogen Receptor Gene Polymorphisms

The association between ERα gene polymorphisms and TMD susceptibility [28] provides genetic evidence supporting a mechanistic role for estrogen signaling in TMD pathophysiology. The XbaI and PvuII polymorphisms may alter ERα expression or function, leading to differential responses to endogenous and exogenous estrogen [37]. The correlation between estrogen-induced IL-6 production and clinical pain intensity [29] further supports the hypothesis that estrogen modulates inflammatory responses in TMD-affected individuals. These findings suggest that genetic variability in estrogen receptor signaling may contribute to the observed heterogeneity in TMD susceptibility and symptom severity among women and may partially explain inconsistent findings across studies.

Although excluded from the main analysis due to its mechanistic (in vitro/ex vivo) design, Ribeiro-Dasilva et al. (2017) provide important biological plausibility for the role of estrogen in TMD. The study demonstrated that estrogen stimulation of monocytes increased IL-6 production, which correlated with clinical pain intensity. These findings support the hypothesis that estrogen may modulate inflammatory pathways relevant to TMD pathophysiology.

4.3. Comparison with Previous Reviews

Previous systematic reviews on hormonal factors and TMD have been limited by narrow inclusion criteria, small sample sizes, and a lack of quantitative synthesis [14,19]. A 2015 review by Bueno et al. [14] concluded that evidence linking estrogen status to TMD was inconclusive, primarily due to methodological heterogeneity and small effect sizes. However, that review did not include recent high-quality studies such as Gaynor et al. (2021) [23] and Mursu et al. (2022) [24], which provide the most robust evidence to date. Our review extends previous work by incorporating recent studies, applying rigorous quality assessment with the Newcastle-Ottawa Scale, and evaluating the certainty of the evidence using GRADE criteria. Our findings suggest that, while evidence remains limited, there is now moderate-quality evidence supporting associations between hormonal contraceptive use, menopausal status, and TMD risk.

4.4. Biological Plausibility

The observed associations are biologically plausible given established mechanisms of estrogen action in the musculoskeletal and pain systems. Estrogen receptors are expressed in TMJ tissues,

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including synovium, fibrocartilage, and subchondral bone, where they regulate chondrocyte proliferation, collagen synthesis, and extracellular matrix turnover [5,6]. Estrogen also modulates inflammatory pathways by inhibiting nuclear factor-κB (NF-κB) signaling and reducing the production of pro-inflammatory cytokines such as IL-6 and TNF-α [38]. In the central nervous system, estrogen influences pain processing through interactions with serotonergic, GABAergic, and opioidergic systems and modulates descending pain-inhibition pathways [39]. Estrogen deficiency or dysregulation may therefore increase susceptibility to TMJ degeneration, inflammation, and central sensitization, all of which are implicated in TMD pathophysiology.

4.5. Clinical Implications

The findings of this review have several potential clinical implications. First, clinicians should be aware that hormonal factors, including hormonal contraceptive use and menopausal status, may influence TMD risk and symptom severity in female patients. Screening for hormonal exposures may aid in risk stratification and personalized treatment planning. Second, women experiencing TMD symptom exacerbation during specific phases of the menstrual cycle or following menopause may benefit from targeted interventions, including pain management strategies, physical therapy, and, potentially, hormonal therapies, although the latter requires further investigation. Third, the genetic evidence linking estrogen receptor polymorphisms to TMD susceptibility suggests that future research on precision medicine approaches that incorporate genetic profiling may improve risk prediction and therapeutic targeting.

However, it is important to emphasize that the current evidence does not support routine use of hormone replacement therapy or modification of hormonal contraceptive use solely for TMD management, as the benefits and risks of hormonal interventions must be carefully weighed in the context of each patient's overall health profile.

4.6. Strengths and Limitations

4.6.1. Strengths

This systematic review has several strengths. First, we conducted a comprehensive literature search across multiple databases, including PubMed, Embase, Scopus, Web of Science, and Google Scholar, minimizing the risk of missing relevant studies. Second, we applied rigorous inclusion criteria that required validated TMD diagnostic criteria (RDC/TMD, DC/TMD, or equivalent), thereby enhancing the reliability and comparability of the findings. Third, we used the Newcastle-Ottawa Scale for quality assessment and GRADE criteria for certainty of evidence, providing transparent and standardized evaluation of study quality and evidence strength. Fourth, we included diverse hormonal exposures, encompassing hormonal contraceptive use, menopausal status, menstrual cycle variation, pregnancy, and genetic polymorphisms, offering a comprehensive overview of the role of estrogen in TMD.

4.6.2. Limitations

Several limitations must be acknowledged. First, the small number of included studies (n=8) and the limited number of high-quality studies (n=2) constrain the strength of conclusions. Second, substantial heterogeneity in exposure definitions (e.g., self-reported vs. biochemically validated hormonal status), outcome measures (e.g., first-onset TMD vs. palpation pain vs. degenerative joint disease), and study designs (prospective cohort, cross-sectional, case-control) precluded quantitative meta-analysis. Third, most studies relied on self-reported hormonal exposures, which are subject to recall bias and misclassification. Fourth, few studies adjusted for important confounders such as body mass index, smoking, psychological factors (anxiety, depression), and pain catastrophizing, all of which are known to influence TMD risk and symptom severity. Fifth, the cross-sectional design of several included studies limits causal inference. Sixth, publication bias cannot be ruled out, as studies with null findings may be less likely to be published. Finally, all included studies were conducted in

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high-income countries (the United States, Finland, Iran, Italy, and Indonesia), limiting generalizability to other populations.

4.7. Implications for Future Research

Future research should prioritize well-designed prospective cohort studies with large sample sizes, biochemically validated hormonal assessments (including circulating estradiol, progesterone, and FSH levels), and standardized TMD diagnostic criteria (DC/TMD). Longitudinal studies tracking hormonal changes and TMD symptom trajectories across reproductive transitions (e.g., menarche, pregnancy, perimenopause, menopause) are needed to elucidate temporal relationships and causality. Interventional studies evaluating the effects of hormone replacement therapy, hormonal contraceptive formulations, and selective estrogen receptor modulators (SERMs) on TMD symptoms are warranted, with careful consideration of potential risks and benefits. Mechanistic studies investigating the molecular pathways linking estrogen signaling to TMJ inflammation, cartilage degradation, and pain processing will enhance understanding of pathophysiology and inform therapeutic targeting. Finally, incorporation of genetic profiling (e.g., estrogen receptor polymorphisms) and metabolomic analyses may facilitate precision medicine approaches and identify subgroups of women most likely to benefit from hormonal interventions.

5. Conclusion

This systematic review of seven studies provides moderate-quality evidence that hormonal factors, particularly hormonal contraceptive use and menopausal/climacteric status, are associated with increased risk and altered clinical features of temporomandibular disorders in women. High-quality studies demonstrated significant associations between hormonal contraceptive use and first-onset TMD, as well as between climacteric status and TMJ palpation pain, crepitus, and degenerative joint disease. Additional evidence supported variation in menstrual cycle-related symptoms and genetic susceptibility mediated by estrogen receptor polymorphisms. However, the limited number of studies, heterogeneity in exposure and outcome definitions, and reliance on self-reported exposures constrain definitive conclusions regarding causality and clinical implications.

Clinicians should consider hormonal factors when evaluating and managing female patients with TMD, and future research should prioritize prospective cohort studies with biochemically validated hormonal assessments, standardized diagnostic criteria, and comprehensive adjustment for confounders. Interventional studies evaluating the effects of hormonal therapies on TMD symptoms are needed to inform evidence-based clinical decision-making and advance precision medicine approaches for this complex, multifactorial disorder.

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