# INTERRELATIONSHIP BETWEEN THE MENSTRUAL CYCLE AND THE PHENOMENA ASSOCIATED WITH ORTHODONTIC TOOTH MOVEMENT: A SYSTEMATIC REVIEW

**Hayat M R M A Almansour**
DDS, Ajman University, 2014

Submitted to the Hamdan Bin Mohammed College of Dental Medicine
Mohammed Bin Rashid University of Medicine and Health Sciences
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Orthodontics
2022

# ABSTRACT

## Interrelationship between the menstrual cycle and the phenomena associated with orthodontic tooth movement: a systematic review

**Hayat Almansour**

**Principal supervisor: Associate Professor Eleftherios G. Kaklamanos**

**Co-Supervisor: Professor Athanasios E. Athanasiou**

**Background:** As female hormone levels affect bone metabolism, the changes encountered during the menstrual cycle may exert an influence on the phenomena associated with orthodontic tooth movement.

**Aim:** To systematically investigate the available evidence from human studies regarding the interrelationship between the menstrual cycle and the phenomena associated with orthodontic tooth movement.

**Materials and Methods:** Search without restriction for published and unpublished literature and hand searching took place. Studies investigating the interrelationship between the menstrual cycle (e.g., specific stage of the cycle, duration of menstrual bleeding, menstrual cycle length, etc.) and the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.) were reviewed. Study retrieval and selection were followed by extraction of relevant data, and bias risk assessment using the Cochrane ROB tool for randomized controlled studies and the Newcastle-Ottawa Scale.

**Results:** From the final records, 6 studies met the inclusion criteria. During menstruation, orthodontic tooth movement was higher. Osteocalcin levels were found to increase as well. Orthodontic pain was found to be affected by the periodic phase of

menstruation and was increased in patients with primary dysmenorrhea. Moreover, fixed orthodontic treatment influences the menstrual cycle length in the first month after bonding but showed no effect on the duration of menstrual bleeding or subsequent menstrual cycle length. The risk of bias assessment revealed shortcomings in certain domains.

**Conclusion:** Menstrual cycle presents interrelationship with the phenomena associated with orthodontic tooth movement and the orthodontist should consider the possible implications.

# DEDICATION

This dissertation is dedicated to my favorite person my best friend, my everything. Thank you for being always there making it all seem easy. You are a dream.

# DECLARATION

I declare that all the content of this thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Hayat M R M A Almansour

Signature:

# ACKNOWLEDGMENTS

First and foremost, praises and thanks to God, the Almighty, for His showers of blessings throughout my research work to complete the research successfully.

I owe my deepest and most sincere gratitude to my thesis supervisor Associate Professor Eleftherios G. Kaklamanos for providing invaluable guidance throughout this research. His dynamism, vision, sincerity and continuous motivation have deeply inspired me. It was a great privilege and honor to work and study under his guidance. I am extremely grateful for what he has offered me. I would also like to thank him for his empathy, support, and genuine passion to teach. I feel extremely fortunate to have had the opportunity to be a student of his.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF APPENDICES

# 1. INTRODUCTION

Orthodontic therapy aims at providing a functional and pleasing occlusal result that is stable, in balance with the overall esthetics of the face (1). Apart from the numerous benefits patients might exhibit some undesirable side effects such as pain, discomfort, anxiety, dietary changes, and even oral tissue damage. Patients may experience stress or psychological changes as a result of these undesirable effects (2-5).

The demand for orthodontic treatment is mainly from adolescent and adult females (1). Females are more susceptible to orthodontic pain than males, an uncomfortable sensation that more than 90% of patients report throughout orthodontic treatment (6, 7). Females reported more intense discomfort than males, which was observed from days 3 to 7 after orthodontic pressures were applied. Furthermore, the pain in women lasted longer (7-9) . It has been proven that physical and psychosocial factors, such as high-density exercise and changes in nutrition, occupation, and lifestyle, are linked to menstruation abnormalities (10, 11). The effects of female gonadal hormones could explain the gender variation in pain perception (12, 13). The follicular phase and the luteal phase are the two separate phases of a female menstrual cycle. Pain sensations changed in different menstrual phases, according to numerous well-founded research (14-16).

The menstrual cycle is a normal physiological alteration that occurs in women on a regular basis. Estrogen is one of the most important sex hormones for maintaining regularity during the female menstrual cycle, as well as for the construction and function of human bone tissue. It has a near-monthly periodicity (17, 18). As orthodontic tooth movement progresses, alveolar bone metabolism plays a significant role. Changes in estrogen levels may affect the movement of teeth, especially in the local environment of alveolar bone, where estrogen plays a critical role in bone

structure modification, bone mass maintenance, and the bone tissue remodeling process (19, 20). Estrogen levels fluctuate regularly during a woman's typical physiological cycle, with low levels during menstruation, a peak during ovulation, and a near-monthly rhythmicity. When estrogen levels are high (during the ovulation period), osteoblast function is active and osteoclast function is low, resulting in a higher rate of osteogenesis than bone loss, which could lead to orthodontic tooth movement inhibition and decreased orthodontic tooth movement. When estrogen levels are low (during the menstrual period), osteoclast function is active and osteoblast function is low, resulting in a rate of bone loss that is greater than the rate of osteogenesis, favoring a high rate of orthodontic tooth movement. Estrogen levels after menopause are low, therefore women in this age group are more susceptible to osteoporosis symptoms (21). As a result, knowing how the menstrual cycle affects tooth movement in orthodontics and evaluating the ramifications could be beneficial to the clinical orthodontist.

In animals, when estrogen and/or progesterone levels are low during estrus cycle, orthodontic tooth movement is seen to increase (22). However, to the best of the authors' knowledge, evidence-based summary of the information regarding the interrelationship between the menstrual cycle and the phenomena associated with orthodontic tooth movement has not been compiled.

# 2. REVIEW OF THE LITERATURE

The underlying principle of orthodontic therapy is that when mechanical pressures are applied to teeth, they trigger a series of biological responses that lead to bone adaptation in a new environment and, as a result, to tooth movement (23). Clinicians have always aspired to understand the fundamental concepts of tooth movement mechanisms in order to reduce treatment time and improve patient satisfaction (24).

## 2.1. Tooth movement and bone physiology

### 2.1.1. Orthodontic tooth movement

When external forces, either intermittent or continuous, are applied to teeth, orthodontic tooth movement occurs because of a variety of biological responses. The periodontal ligament distorts and the bone bends as a result of these loads, changing the mechanical environment of the teeth and surrounding tissues (24). In an attempt to explain the mechanisms involved in tooth movement related to orthodontic therapy, numerous theories have been proposed in the literature (23). In general, hypotheses have focused on the fact that the stimuli target the bone and the periodontal ligament (25). These orthodontic tooth movement hypotheses are still theoretical to some extent, but the histology evidence is indisputable (26). In order to explain and forecast tooth movement, physicians have traditionally relied on the pressure tension theory, which is based on over a century of observations (27). Carl Sandstedt, a Swedish dentist, conducted in 1904 the pioneering studies on dogs that are the foundation of our present understanding of the phenomena associated with the movement of teeth. Sandstedt found in his seminal tests that applying force to the periodontal ligament and alveolar bone caused tissue changes (27).

Following this, Oppenheim in 1911, discovered that as a teeth move, the periodontal ligament forms a "pressure side" and a "tension side." (27). According to Schwarz’s

studies in 1932, orthodontic forces should not be "higher than the pressure in the capillary blood," (27). Due to the compression of periodontal fibers, the change in blood flow leads to reduced oxygen supply in the pressure side and a higher oxygen supply in the tension side. On the pressure side, alveolar bone resorption is visible, while on the tension side, new bone apposition is observed (27). Compression can cause tissue necrosis by deprivation of oxygen supply in the periodontium if the capillary blood pressure is surpassed (28). Reitan in 1957 discovered that hyalinization might develop in the periodontal ligament if even light forces are applied. Additional hyalinization occurs after force application when roots are shorter, resulting in higher pressure development (27).

The bone bending theory describes the phenomena associated with the transfer of forces applied to teeth when an orthodontic appliance is placed (29). The periodontal ligament and osseous tissue are mechanically perturbed as a result of these stresses leading to bending of bone. Bone has been discovered to be more elastic than other tissues, bending significantly more easily in response to force (30). When a force is applied to a tooth, the tooth is displaced several times greater than the width of the periodontal ligament, and bone bending is necessary for this to happen (26). Researchers were able to explain clinical observations such as the rapidity of tooth movement toward an extraction site or in thin bone, as well as the relative slowness of en-masse tooth movement, using this theory. This theory could also help explain why children's teeth move faster than adults' since their bones are more flexible and less calcified (26). Orthodontic tooth movement has also been linked to potential electrical signals created following alveolar bone bending (1). In the 1960s, there was a lot of interest in piezoelectricity as a bone remodeling stimulant. It was discovered that crystalline structure distortion produced tiny electrical charges, which could be responsible for

signaling osseous changes caused by mechanical force application. Clinical trials using pulsed magnetic fields to accelerate the rate and amount of tooth movement have been conducted based on this notion (1).

2.1.2. Cell types in bone

Bone is a dynamic tissue that responds to mechanical forces by remodeling. The cells that carry out this response are scattered throughout the bone, each performing unique duties such as activating cells, resorbing bone, and depositing new bone matrix to fulfill the skeleton's role (25). Osteoblasts, osteoclasts, and osteocytes are the three primary types of cells in the alveolar bone that respond to orthodontic stimuli (31). Osteoblasts are mononuclear, bone-forming cells that can be detected on the surface of the bone at apposition sites (25). They secrete bone matrix and type I collagen. Furthermore, osteoblasts respond directly to strain from orthodontic stimuli (23). Although osteoblasts are important in maintaining the integrity of alveolar bone during tooth movement, they are not the cells that determine how quickly a tooth moves (25). The teeth can only move towards areas of resorbed bone after the initial movement in the periodontal ligament space. The osteoclasts, the second type of osseous tissue cell, play a critical role. Osteoclasts are specialized macrophages that develop from multiple monocytic progenitor cells fusing into a single multinucleated cell. In fact, the rate of bone resorption and, as a result, the rate of tooth movement is determined by the osteoclasts (25). The osteocytes, the third type of cell, are mature osteoblasts embedded in osseous lacunae. Proprioceptive and responsive characteristics are present in these cells (23). To some extent, the precise function of osteocytes is unknown, however they have been discovered to coordinate the activation of osteoblasts and osteoclasts (31).

The bone lining cell is a fourth cell type that is important in bone protection and the maintenance of bone fluids. These cells could possibly play a role in the propagation of

the activation signal that triggers bone resorption and remodeling. Finally, osteoprogenitor cells are a type of stem cell that is responsible for producing osteoblasts (23). Colony-Stimulating Factor (CSF), Receptor Activator of Nuclear Factor-Kappa B Ligand (RANKL), Osteoprotegerin (OPG), and Bone Morphogenic Proteins (BMPs) are bone soluble factors that govern osteoclast differentiation (23). Osteocytes in the alveolar bone and osteoblasts in the periodontal ligament produce them all. The differentiation of osteoclasts is aided by CSF, RANKL, and its receptor, RANK. The crucial molecule in the maturation of osteoclasts is RANKL in particular. Osteocytes are the primary producers of RANKL in the bone, and their release of soluble RANKL promotes osteoclastogenesis. This enhances its interaction with osteoclast precursors, causing differentiation and activation to occur. As a result, osteocytes in alveolar bone may be responsible for the increase in orthodontic tooth movement-induced RANKL expression (23).

2.1.3. Bone remodeling cycle

Throughout life, bone tissue maintains its integrity and responds to changes through a continuous turnover, a process known as bone remodeling. Bone remodeling in orthodontic tooth movement consists of bone mass loss at periodontal ligament pressure areas and bone apposition at tension areas. This sequence of events is the central theme of the pressure-tension hypothesis (32).

The bone remodeling cycle includes three phases: the resorption phase, the reversal phase and the formation phase. During the resorption phase, resorption and digestion of old bone by the osteoclasts occurs. Then mononuclear cells appear during the second phase, the reversal phase. The resorbed bone is completely replaced by a layer of new bone carried out by the osteoblasts during the formation phase. Hormones and a variety of other proteins appear to regulate bone integrity. The bone remodeling cycle is

governed by both systemic and local factors. Thyroid hormones are significant systemic regulators, with parathyroid hormone (PTH) being the most important, in addition to calcitriol, glucocorticoids, growth hormones, and sex hormones (33). As long as the balance between resorption and bone formation stays constant, skeletal homeostasis is maintained (31).

Bone remodeling units (BRU) are the fractions of bone that are renewed at any time during remodeling. In a process taking few weeks, the bone in the activated BRU is first digested by osteoclasts. After that, osteoblastic bone growth replaces the missing bone, which might take up to 3-4 months for a packet. This explains why, in the case of menopause and estrogen deprivation, greater resorption, even when coupled by increased bone production, can result in overall bone loss (34).

Bone mass is mostly determined by the period preceding and following puberty. During puberty and years of growth spurts, approximately 25% of calcium is deposited in the skeleton (35). High calcium intake, greater food absorption via the intestine, and lower bone resorption are all linked to increased calcium bone retention (36). The latter phenomenon is thought to be caused by an increase in estrogen levels (37, 38). Girls appear to gain more skeletal mass during their pubertal period than is required for their level of physical work. The excessive increase in estrogen levels during puberty has been proposed to lower the remodeling threshold, resulting in less bone resorption while modeling and longitudinal growth continue (37, 38). During the pubertal phase, males gain bone primarily on periosteal surfaces, whereas females gain bone primarily on endocortical surfaces (39). Bone added to endocortical surfaces has a lower impact on bone strength than bone added to periosteal surfaces. As a result, it is possible that the human female skeleton acquires calcium in excess of its immediate needs during puberty as an adaptation mechanism for the needs of subsequent reproductive cycles

rather than for structural reinforcement. This phenomenon appears to be shared by all vertebrates and is not limited to mammals.

**2.2. Hormones and their effect on bone**

Estrogens, thyroid hormones, calcitonin, and other hormones are considered as important regulators of calcium homeostasis. They regulate RANKL and OPG expression and secretion. RANKL is a cytosine that is released by bone marrow cells, osteoblasts, and osteocytes and is involved in the development and differentiation of osteoclasts. RANK is the receptor for RANKL on osteoclast precursors and is part of the RANK/RANKL/OPG signaling cascade, as previously discussed. The binding of RANKL to RANK increases the differentiation of osteoclasts and, as a result, bone resorption (40).

2.2.1. Estrogens

Estrogens are the primary female sex hormones produced by the endocrine system and distributed in local tissues and the bloodstream. Estrogens occur naturally in three major forms: estrone $E_1$, estradiol $E_2$, and estriol $E_3$. Among the most significant hormones, estradiol is produced by the ovaries, and is responsible for regulating sexual and reproductive activities (41). Estradiol and estrone are the most dominant estrogens in adult women, while estradiol is the main estrogen in pregnant females (42-44). During puberty, estrogens cause considerable changes in the female body, such as growth and development of the female sex organs. Furthermore, they aid in the development of mammary ducts and glands noted during the same time period. Estrogens have an effect on bones because they regulate osteoclastic activity and stimulate osteoblastic activity, making them necessary for optimal bone mineralization (45).

Estrogen levels are widely known to play an important function in bone mass preservation (46). Human cells have been found to have estrogen receptors (47) and

several lines of evidence suggest that estrogen inhibits bone remodeling by preventing osteoclastogenesis in marrow precursors and inducing the Fas/FasL pathway, which leads to osteoclast death (48, 49). Estrogen also inhibits bone resorption via influencing the receptor activator of nuclear factor-Kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway as well as the production of several pro-resorptive cytokines (e.g. IL-1, IL-6, IL-7, TNF) (50-56). However, estrogen also has a direct effect on osteoblastic lineage cells, which contributes to bone preservation (57, 58).

The decrease in estrogen levels during menopause is critical for changes development in the osseous tissues (59). Estrogen's osteoprotective actions are mediated through alpha receptors (ERα) in both osteoblasts and osteoclasts (60). Osteoclast ERα deletion causes an increase in osteoclast proliferation and survival, which leads to osseous loss (48). In terms of bone deposition, activation of the ERα of osteoblasts increases bone mineral density through upregulating OPG and Interleukin-6. The absence of estrogens has also been shown to have negative effects on the quality of freshly produced bone (61, 62). Estrogen insufficiency may impair bone matrix development and impact the early phases of bone formation by lowering the levels of key proteins such osteogenin and bone morphogenic proteins (61). Histomorphometric data also revealed a decrease in osteoblast numbers, as well as further unfavorable impacts on bone production in the later stages (62). As a result of the lack of estrogens, osteoclastogenesis and bone resorption would increase, as well as the amount of trabecular bone and the quantity of trabeculae in the alveolar processes, leading in faster tooth movement (63-65).

Estrogen levels fluctuate throughout the menstrual cycle, with the lowest levels occurring during menstruation and gradually increasing during the follicular phase, peaking a few days before ovulation. Estrogen levels drop following ovulation, despite

the fact that estrogen production is kept at a low level during the majority of the luteal phase before plummeting even further and reaching a nadir during menstruation (66).

2.2.2. Progesterone

Progesterone is a steroid sex hormone as well. It's in charge of the endometrium's progestational alterations. Progesterone supports breast development in a complimentary manner to estrogens. Progesterone is also thermogenic, which means it contributes to the 0.5 degree increase in baseline temperature that some women experience following ovulation. It has also been demonstrated that progesterone has bone-protective properties (67). These findings appear to be mediated directly by osteoblast progesterone receptors (68), in addition to indirectly acting as a glucocorticoid receptor ligand (67, 69). Furthermore, progesterone's inhibitory effect on metalloproteinase may play a role in bone matrix modulation (70, 71).

**2.3. Menstrual cycle**

The ovarian cycle and the uterine cycle, i.e., the physiological cycle of orderly shedding of the endometrial lining of the uterus, correspond to the menstrual cycle's typical changes taking place in the ovarian follicles. There are three phases to both cycles. The ovarian cycle is split into the follicular, ovulation, and luteal phases, while the uterine cycle into the menstruation, proliferative, and secretory phases (66, 72).

The number of days between the first day of menses (bleeding) and the start of the next cycle menses corresponds to the length of the menstrual cycle. The majority of cycles last between 25 and 30 days (66).

2.3.1. Phases of the ovarian cycle

Ovulation separates two distinct periods in the ovarian menstrual cycle (Figure 1). The follicular phase lasts from the first day of menstruation through the day of ovulation. The luteal phase begins after ovulation and lasts until the following menstruation (72).

The follicular phase begins on the first day of menstruation, when the body begins to prepare the oocytes for a prospective pregnancy. The levels of Follicle Stimulating Hormone (FSH) rise, stimulating the oocytes. The oocytes are encased in a sac called a follicle, which lends this phase its name. The Follicle Stimulating Hormone also stimulates the follicles to create estradiol, which inhibits the anterior pituitary gland's release of the Luteinizing Hormone (LH). Follicular selection occurs between days 5 and 7 of the menstrual cycle, allowing only one follicle to ovulate while the others undergo atresia. There are three stages to the follicular phase: early, medium, and late. The early follicular phase lasts from the first to the fourth day of menstruation, followed by the middle phase (days 5 to 7) and the late phase (days 8 to 12). Estrogen levels are at their peak in the late phase (66, 72).

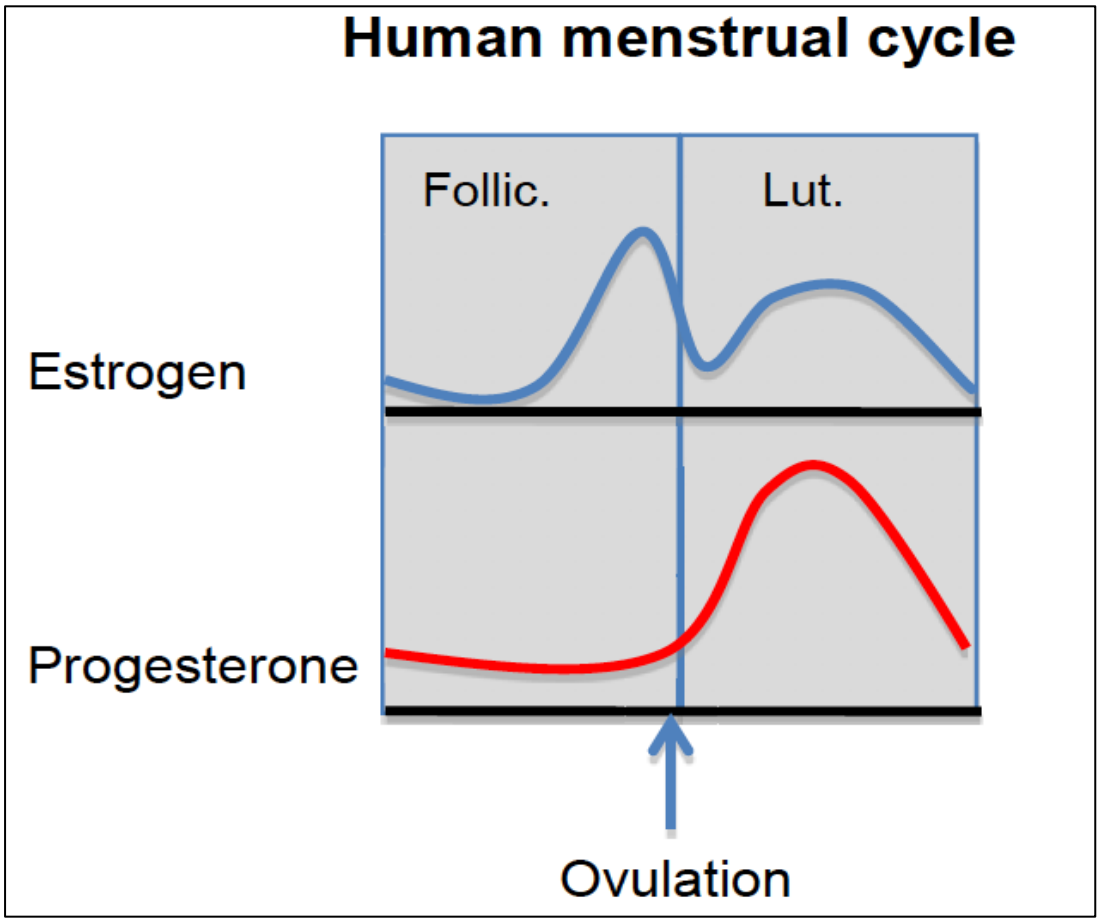



**Figure 1.** The human menstrual cycle [from Lebron-Milad and Milad, 2018].

The mature oocyte is discharged from the ovarian follicles into the oviduct during the

following step of the ovarian cycle, ovulation. Estradiol levels reach a particular threshold at this stage of the ovarian cycle, over which the LH suppressing effect seen during the follicular phase is reversed, resulting in an LH surge caused by the production of a substantial amount of LH. When the oocyte reaches a certain level of estradiol, the effect is reversed, and estrogen encourages the synthesis of a substantial amount of LH. The LH surges cause the oocyte to mature and the follicle wall to weaken in the ovary, allowing the fully grown follicle to release the secondary oocyte (66, 72). The luteal phase is named after the transformation of the follicular cavity into a corpus luteum, which continues to produce estrogen and considerable levels of progesterone. Women's average total body temperature is consistently 0.5°C higher in this phase than in the follicular phase (72).

2.3.2. Phases of the uterine cycle

Menstruation, proliferative phase, and secretory phase are the three phases of the uterine cycle (66).

Menstruation occurs when the endometrial lining of the uterus sheds, resulting in menstrual bleeding, period, or menses. It lasts about 5 days on average, and estrogen and progesterone levels are low during this time. During menses, the average blood loss is 35 ml, with a range of 10 to 80 ml considered typical (66).

The second phase of the uterine cycle is the proliferative phase, during which the endometrial lining of the uterus proliferates due to an increase in estrogen levels. Estradiol levels rise as the ovarian follicles mature, triggering the formation of the proliferative endometrium. Estradiol also causes the cervical crypts to produce mucus, resulting in vaginal discharge (66).

The secretory phase is the final stage of the uterine cycle and corresponds to the luteal phase of the ovarian cycle. The corpus luteum produces progesterone during this stage,

which is necessary to prepare the endometrium for blastocyst implantation. Progesterone is also important in the early stages of pregnancy because it causes an increase in uterine blood flow, an increase in uterine secretions, and a decrease in smooth muscle contractile activity. As previously stated, it causes a 0.5°C increase in a female's basal body temperature over the previous phases.

### 2.4. Hormonal fluctuations during the menstrual cycle and orthodontic tooth movement

The goal of orthodontic treatment is to provide a functional, stable, and aesthetically pleasing occlusion that is in harmony with overall facial esthetics (1). According to studies, the majority of patients seeking orthodontic treatment are adolescent females (73). Furthermore, increased awareness of the benefits of a functional occlusion and a pleasing appearance has resulted in an increase in the number of adults seeking orthodontic treatment (74). One in every three orthodontic patients in the United States is an adult, with females making up the majority (75).

Because orthodontic tooth movement is achieved through changes in the balance of alveolar bone resorption and formation, it could potentially be modulated by any development affecting the relevant cellular and bimolecular networks (76, 77). Hormonal variations, particularly estrogens, that occur normally in healthy adolescent and adult females during the menstrual cycle may further influence bone metabolism on a regular basis (59). As a result, knowing how the menstrual cycle affects orthodontic tooth movement and evaluating the ramifications could be beneficial to the clinical orthodontist.

However, to the best of the authors' knowledge, evidence-based summary of the information regarding the interrelationship between the menstrual cycle and the phenomena associated with orthodontic tooth movement has not been compiled.

# 3. AIM

## 3.1. Aim of the systematic review

To systematically investigate the available evidence from human studies regarding the interrelationship between the menstrual cycle (e.g., specific stage of the cycle, duration of menstrual bleeding, menstrual cycle length), etc. and the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.).

## 3.2.Objectives of the systematic review

To retrieve information from human studies regarding the interrelationship between the menstrual cycle (e.g., specific stage of the cycle, duration of menstrual bleeding, menstrual cycle length), etc. and the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.).

## 3.3. Null hypothesis

There is no difference in the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.). between the various stages of the menstrual cycle.

There is no difference in various characteristics of the menstrual cycle (e.g., duration of menstrual bleeding, menstrual cycle length, etc.) between females subjected to orthodontic tooth movement and control groups.

## 3.4.Alternative Hypotheses

There is a difference in the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.). between the various stages of the menstrual cycle. There is a difference in various characteristics of the menstrual cycle (e.g., duration of menstrual bleeding, menstrual cycle length, etc.) between females subjected to orthodontic tooth movement and control groups.

# 4. MATERIALS AND METHODS

## 4.1 Protocol development

The current review is based on a specific protocol that was developed and piloted in accordance with the PRISMA-P statement guidelines (78). In addition, conduct and reposting The Cochrane Handbook for Systematic Reviews of Interventions was followed (79) as well as the PRISMA declaration (80), respectively.

## 4.2 Eligibility criteria

The selection criteria, followed the PICOS approach, and were the following for the domains of study design, participants' characteristics, intervention characteristics and principal outcome measures:

### 4.2.1.Types of study design

Studies included were prospective controlled studies investigating the interrelationship between the menstrual cycle (e.g., specific stage of the cycle, duration of menstrual bleeding, menstrual cycle length), etc. and the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.) were reviewed. Animal studies, ex vivo, in vitro, in silico, non-comparative research (case reports and case series) and reviews (traditional reviews, systematic reviews as well as meta-analysis) were excluded from the present investigation. The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network) available from http://www.sign.ac.uk (Appendix I).

### 4.2.2.Types of participants

The included studies involved healthy female humans (with menstrual cycle) undergoing orthodontic tooth movement.

4.2.3.Types of interventions

The included studies involved orthodontic force application in various stages of the menstrual cycle.

4.2.4.Types of outcome measures

The studies had to report either on menstrual cycle characteristics (e.g., specific stage of the cycle, duration of menstrual bleeding, menstrual cycle length), etc. or on the phenomena associated with orthodontic tooth movement (e.g., rate of tooth movement, pain, biomolecule levels, etc.).

**4.3. Information sources and search strategy**

For each database, the principal investigator devised specific search strategies. These were based on the MEDLINE strategy but were modified to account for differences in controlled vocabulary and syntax rules for each database. The following electronic databases were searched (Appendix II): MEDLINE via PubMed, CENTRAL, Cochrane Systematic Reviews, Scopus, Web of Science ™ Core Collection, Arab World Research Source, Clinical Trials registry and ProQuest Dissertations & Theses Global databases are all available.

There were no restrictions placed on the language, date or status of publication. In addition, efforts were made to obtain conference proceedings and abstracts where possible and the reference lists of all the eligible studies for additional records were searched.

**4.4. Study selection**

The main investigator and the thesis principal supervisor independently evaluated the retrieved records for inclusion They were not blinded to the authors' identities, institutions, or research findings. The full-text of the records considered to meet the inclusion criteria by either reviewer were obtained and independently assessed, while

disagreements were resolved through discussion with the co-supervisor.

### 4.5. Data collection and data items

The primary investigator and the thesis principal supervisor extracted data independently, and any disagreements were resolved through discussion with the co-supervisor. To record the desired information, data collection forms were used.

a.The study's bibliographic information

b.Details about the study's design and verification of study eligibility

c.Subject characteristics (where available number, age, weight)

d.Tooth movement model

e.Details on outcomes characteristics and results

f.Additional information: a prior sample size calculation, error of the method assessment

If clarifications or additional material were required regarding the published data, attempts would be made to contact the corresponding authors.

### 4.6. Risk of bias in individual studies

The risk of bias in the included randomized controlled trials was assessed independently and in duplicate by the main investigator and the thesis principal supervisor, with the RoB2 tool for RCTs (79). The risk-of-bias VISualization (robvis) web application was then used to enter the assessments (81).

For the non-randomized studies the risk of bias was assessed using the Newcastle-Ottawa Quality Assessment scale for Cohort Studies (82). The Newcastle-Ottawa Quality Assessment scale for Cohort studies includes the following domains:

1: Was the exposed cohorts representative of average child in the community?

2: Was selection of non-exposed cohort drawn from the same community as the exposed cohort?

3: Was the exposure ascertained ?

4: Was the outcome of interest present at start of study?

5: Was the groups comparable in regard to age and sex?

6: Were there additional risk factors more than two, other than age and sex?

7: Were outcomes assessed using independent blinding or record linkage?

8: Was follow up long enough for outcome to occur?

9: Were the follow up cohort adequate or subjects lost to follow up unlikely to interduce bias?

After entering the data extraction form the information reported in each study, every domain would receive a judgment of poor, fair or good risk of bias (82).

Disagreements were resolved through discussion in all of the processes mentioned above; kappa statistics were not calculated as a result of the relevant suggestions (79).

### 4.7. Summary measures and synthesis of results

Despite the fact that a synthesis of the results was planned in accordance with the research protocol, it was not carried out in the end due to a lack of sufficient data.

### 4.8. Additional analyses

As an insufficient number of trials was identified, analyses for “small-study effects” and publication bias (79) were not possible. Furthermore, subgroup analyses and meta-regression was not carried out due to the lack of adequate amount of data.

# 5. RESULTS

## 5.1. Study selection

Figure 2 shows the flowchart of records as they go through the review process. The data search took place in February 2022. Initially 43 records were identified through the data base and 11 records were excluded as duplicates. Furthermore, 23 records were excluded as irrelevant and another 3 as involving animal studies (83-86). Finally, 6 records were included in the systematic review(3, 86-90).

## 5.2. Study characteristics

Tables 1 and 2 present the features of the retrieved studies. The studies were published between 2014 and 2017, and were 2 randomized controlled trials (86, 87) and 4 cohort studies (3, 88-90).

The two randomized controlled trials (86, 87) investigated the effects of orthodontic force applied at different stages of menstrual cycle in terms of tooth movement rate in adolescent females aged between 14 and 18 years old (87), as well as the changes in estrogen (E2), osteocalcin (OCN), receptor activator of nuclear factor-κ B ligand (RANKL), and osteoprotegerin (OPG) levels in the gingival crevicular fluid (GCF) in adult females aged 18 to 28 years old (86). Both studies involved individuals with maxillary premolar extractions.

Wang et al. (87) was a split-mouth randomized controlled study. After extraction of the first maxillary premolar, the left and right maxillary canines of the same patient were randomly grouped into the menstrual period activation group and the ovulation activation group. All 12 patients were being treated with the MBT™ brackets and underwent alignment until a 0.018 × 0.025 stainless steel wire could be fully inserted. In the menstrual phase activation side, a 150g distally directed force was applied on the

canine with a NiTi spring, attached on mini screws, on the first day of the menstrual period and for a period of 4 weeks. In the ovulation phase activation side, the same was done on the first day of ovulation (measured by ovulation test strip) and for a period of 4 weeks. Alginate impressions were taken on the day of force application and 4 weeks later. The distance of the canine apex and the mesiobuccal cusp of the maxillary first molar on the same side was measured. Each measurement was performed 6 times and averaged.

In the Yang et al. (86) randomized study all patients were being treated with the MBT™ brackets and underwent alignment until a 0.018 × 0.025 stainless steel wire could be fully inserted. Six patients were randomly assigned to the menstrual activation group and six patients to the ovulation activation group. In the menstrual activation group, a 150g distally directed force was applied on the right canine with a NiTi spring, attached on mini screws, on the first day of the menstrual period. In the ovulation activation group, a 150g distally directed force was applied on the right canine with a NiTi spring, attached on mini screws, on the first day of ovulation (measured by ovulation test strip). Periodontal scaling was performed on all patients 1 week before force application and oral health advise was given. The gingival crevicular fluid from the distal side of the right canine was sampled before force application on day 0 (T0), as well as at 15 (T1), 30 (T2), and 45 days (T3) later. Each sampling was repeated three times and averaged.

Three studies (3, 88, 90) focused on the overall theme of pain experience by the application of orthodontic forces.

Long et al. (3) investigated the effect of applying orthodontic force during the follicular or the luteal phase of the menstrual cycle following initial archwire placement. A total of 76 consecutive adult female patients were recruited and depending on their menstrual

cycle stage on the day of bonding they were assigned to a follicular or a luteal phase intervention group. Orthodontic pain levels were assessed by a visual analogue scale (VAS) on days 1, 2 and 3 following initial engagement of a .012" NiTi archwire.

Similarly, Ileri et al. (90) investigated the effect of applying orthodontic force during the follicular or the luteal phase of the menstrual cycle on canine distalization with lacebacks. A total of 48 consecutive adult female patients were recruited and depending on their menstrual cycle stage on the day of bonding they were assigned to a follicular or a luteal phase intervention group. Orthodontic pain levels were assessed by a visual analogue scale (VAS) on days 1 and 2 following initial activation.

Ye and coworkers (88) aimed to examine whether a relationship exists between primary dysmenorrhea (PD) and pain experience by the application of orthodontic forces. Orthodontic treatment was initiated within one week following the end of the previous menstrual period. Orthodontic pain levels were assessed by a visual analogue scale (VAS) on days 1, 2, 4, 7, 14 and 28 following initial engagement of a .014" NiTi archwire.

Finally, Duan and coworkers (89) investigated the effect of bonding braces and engaging a .012" NiTi archwire on menstrual cycle length, duration of menstrual bleeding and amount of blood lost, in adult female patients. Data were collected over six consecutive cycles from a group of 164 women with normal cycles.

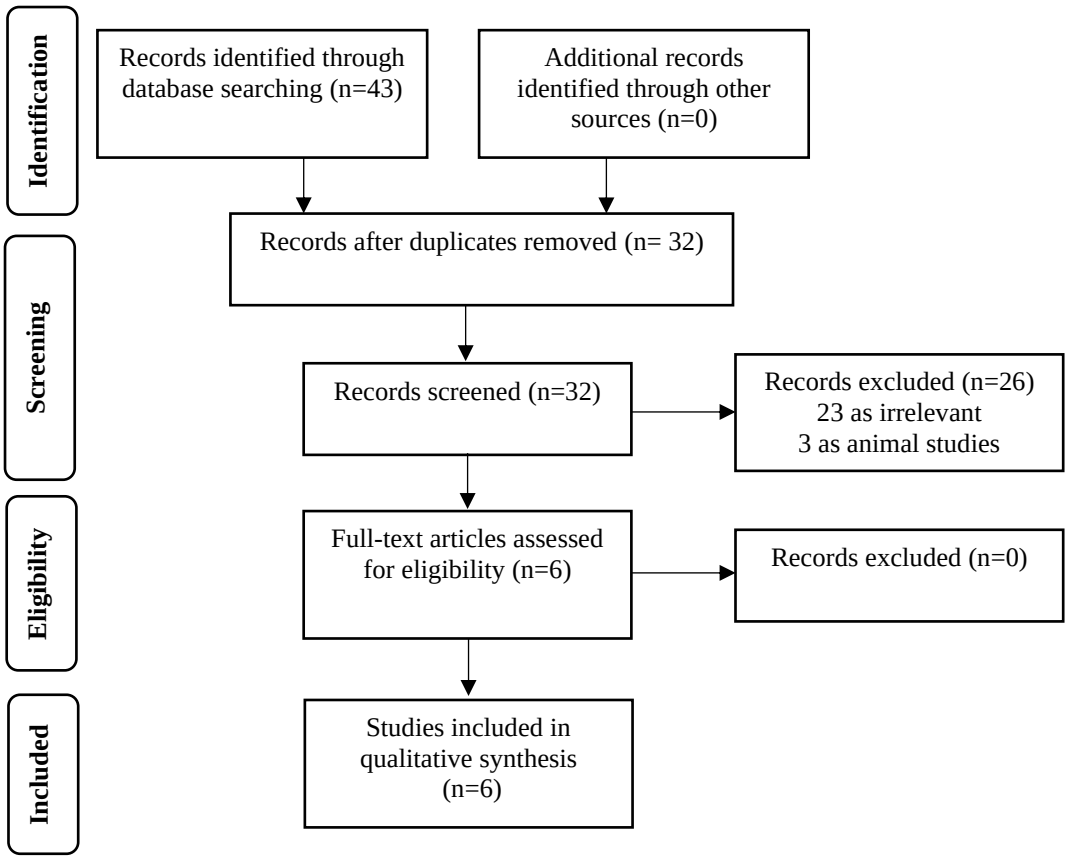



**Figure 2.** Flowchart of records through the reviewing process.

**Table 1.** General characteristics of the studies included in the systematic review.

| Study | Intervention characteristics | Outcomes & assessment methods | Additional information |
|---|---|---|---|
| **Duan et al. 2016**<br>Cohort study | Initial engagement of a .012" NiTi archwire<br>*Orthodontic treatment group*<br>*No treatment group* | **Menstrual cycle characteristics**<br>menstrual cycle length, duration of menstrual bleeding and amount of blood lost | Power calculations: Yes |
| **Ileri et al. 2016**<br>Cohort study | Extractions of Mx first premolars and canine distal movement with lacebacks<br>*G1: The menstrual cycle's follicular phase*<br>*G2: the menstrual cycle's luteal phase* | **Orthodontic pain**<br>VAS; days 1, 2 following initial activation<br>**Verbal rating scale** | Power calculations: Yes |
| **Long et al. 2017**<br>Cohort study | Initial engagement of a .012" NiTi archwire<br>*G1: The menstrual cycle's follicular phase*<br>*G2: the menstrual cycle's luteal phase* | **Orthodontic pain**<br>VAS; days 1, 2 and 3 following initial engagement | Power calculations: Yes |
| **Wang et al. 2014**<br>Randomized controlled study<br>Split mouth | Extractions of Mx first premolars and canine distal movement on a 0.018×0.025 SS wire<br>150g distally directed force was applied on the canine with a NiTi spring, attached on mini screws<br>*G1: menstrual phase activation side*<br>*G2: ovulation phase activation side* | **Rate of tooth movement**<br>Measured on casts; distance of the canine apex and the mesiobuccal cusp of the maxillary first molar on the same side after 4 weeks of force application | Power calculations: NM |
| **Ye et al. 2014**<br>Cohort study | Initial engagement of a .014" NiTi archwire<br>*3 groups according to primary dysmenorrhea* | **Orthodontic pain**<br>VAS; days 1, 2, 4, 7, 14 and 28 following initial engagement | Power calculations: NM |
| **Yang et al. 2014**<br>Randomized controlled study | Extractions of Mx first premolars and canine distal movement on a 0.018×0.025 SS wire<br>150g distally directed force was applied on the canine with a NiTi spring, attached on mini screws<br>*G1: menstrual phase activation group*<br>*G2: ovulation phase activation group* | **E2, OCN, RANKL OPG levels in GCF**<br>Sampling on the distal side of the canine on day 0 (T0), as well as at 15 (T1), 30 (T2), and 45 days (T3) later | Power calculations: NM |

ES: Estrogen; G: group; GCF: gingival cervical fluid; NiTi: Nickel-titanium; NM: not mentioned; OCN: osteocalcin; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor- κB ligand, SS: stainless steel; VAS visual analogue scale

**Table 2.** Sample characteristics in the studies included in the systematic review.

| Study | Inclusion and exclusion criteria | Analyzed sample |
|---|---|---|
| **Duan et al. 2016**<br>Cohort study | **Inclusion criteria:** MCL & DMB fluctuates no more than 3 days and 1 day respectively for at least 1 year, no dysmenorrhea or other reproductive system disease, no oral oral diseases other than teeth irregularity.<br>**Exclusion criteria:** smokers or alcoholic, suffering from psychological diseases, suffering from systematic diseases, using medications, requires orthognathic surgery and using contraceptives. | **164 adult female patients**<br>Aged 18-40 years |
| **Ileri et al. 2016**<br>Cohort study | **Inclusion criteria:** American Society of Anesthesiologists (ASA) physical status, regular menstrual cycles, scheduled to undergo the extraction of two upper first premolars<br>**Exclusion criteria:** history of psychiatric treatment, mild-to-severe periodontal disease, a history of orthodontic treatment, difficulty in communication, irregular menstrual cycles, amenorrhea, pregnancy, history of combined oral contraceptive use, pain in any part of the body on the appointment day, and concomitant use of an analgesic within the previous 24 h | **48 female patients**<br>Aged 16-20 years |
| **Long et al. 2017**<br>Cohort study | **Inclusion criteria:** good general health, regular menstrual periods<br>**Exclusion criteria:** Previous orthodontic Tx, recent orofacial pain, pregnancy, recent medical history, uses contraceptives. | **76 female patients**<br>age >18 years |
| **Wang et al. 2014**<br>Randomized controlled study<br>Split mouth | **Inclusion criteria.** have menarche, and regular menstrual cycle, Class I, requiring maxillary first premolar extraction<br>**Exclusion Criteria:** Severe dentition crowding, Canine relationship was of significant Class II and III or crossbite relationship. | **12 female patients**<br>14-18 years old |
| **Ye et al. 2014**<br>Cohort study | **Inclusion criteria:** mild crowding <4 mm in each jaw, no extraction, no other malocclusions, no crowding, no pregnancy or abortion, regular menstrual cycle, with experienced painful menstrual cycle<br>**Exclusion criteria:** Had previous orthodontic Tx, had analgesic 3 days prior orthodontic Tx, recent toothache, excessive anxiety according to the T-AI ≥57, abnormal CPT <3 sec or >60 sec and abnormal pain tolerance >5 min. | **124 female patient**s<br>age >18 years |
| **Yang et al. 2014**<br>Randomized controlled study | **Inclusion criteria:** age 18 to 28 years old, good physical condition, not pregnant, no systemic diseases, no use of hormones or immunomodulators in the past 6m, regular physiological cycles in the past 12m, good oral hygiene/periodontal conditions, no history of orthodontic treatment. | **12 female patients**<br>age 18 to 28 years old |

Tx: treatment; T-AI: Trait-Anxiety Inventory; CPT: cold pressor test;; m: months; MCL: menstrual cycle length; DMB: duration of menstrual bleeding

### 5.3. Risk of bias within studies

The risk of bias assessment for all randomized studies showed some concerns regarding the randomization process (Figure 3).

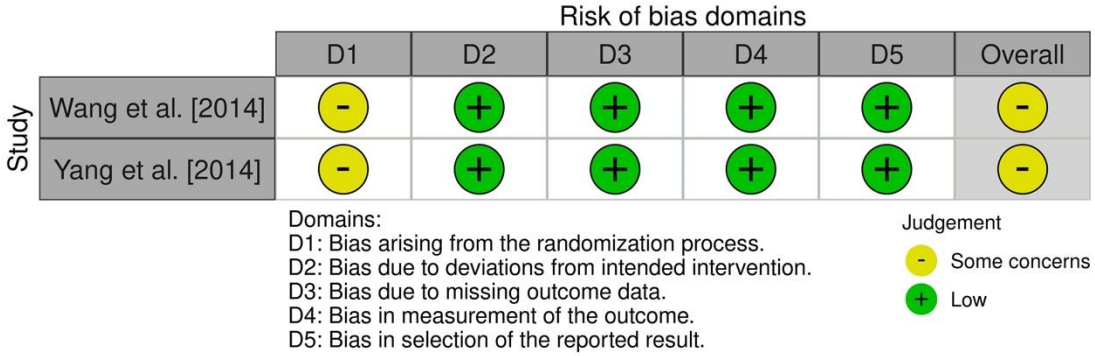



**Figure 3.** Risk of bias assessment for the randomized studies.

The summary of risk of bias assessment for the non-randomized studies is presented in Table 3. All 4 included studies received the maximum score.

**Table 3.** Summary of risk of bias assessment for the non-randomized studies

| Quality assessment criteria | Duan et al. [2016] | Ileri et al. [2016] | Long et al. [2017] | Ye et al. [2014] |
|---|---|---|---|---|
| Representativeness of exposed cohort? | * | * | * | * |
| Selection of the non-exposed cohort? | * | * | * | * |
| Ascertainment of exposure? | * | * | * | * |
| Demonstration that outcome of interest was not present at start of study? | * | * | * | * |
| Study controls for age/sex? | * | * | * | * |
| Study controls for at least 3 additional risk factors? | * | * | * | * |
| Assessment of outcome? | * | * | * | * |
| Was follow-up long enough for outcome to occur? | * | * | * | * |
| Adequacy of follow-up of cohorts? | * | * | * | * |

### 5.4. Results of individual studies

Regarding the effects of orthodontic force applied at different stages of menstrual cycle, it was shown that teeth with the application of orthodontic force at the menstrual period, when estrogen levels are low, move faster than teeth with the application of orthodontic force at the ovulatory phase (87). Yang et al. (86) observed that E2 and the ovulation phase group had significantly greater OCN levels than the menstrual period group ($p<0.05$), promoting faster movement of teeth. No significant differences were found in RANKL and OPG levels, as well as the RANKL/OPG ratio, were noted between the two groups ($p>0.05$).

Pain levels associated with the application of orthodontic forces were higher in patients in the luteal phase than those in the follicular phase of the cycle (3, 90). Ye and coworkers (88) reported that there was a positive correlation between the severity of primary dysmenorrhea and the intensity of orthodontic pain. Females who experienced more menstrual pain tended to experience orthodontic pain with greater intensity and for a longer period.

Finally, Duan et al. (89) observed that the length of the menstrual cycle may be affected by fixed orthodontic treatment in the first month after bonding, but there was no effect during follow-ups. When compared to baseline, the menstrual cycle length of the first menstrual cycle was considerably lengthened by $2.1 \pm 0.5$ days ($p=0.003$). No differences were shown for the duration or amount of bleeding.

### 5.5. Additional analyses

Subgroup analyses, as well as analysis for "small-study effects" and publication bias, were not possible.

# 6. DISCUSSION

## 6.1. Summary of available evidence

Adolescent and adult females make up the majority of orthodontic patients (1). Fluctuation of hormone levels during the menstrual cycle may affect alveolar bone metabolism (91). Tooth movement was stronger during the menstrual part of the cycle, when estrogen and/or progesterone levels are lower, according to the data from the human studies retrieved throughout the evaluation. Pain levels associated with orthodontic forces were lower during the same period. Females who experience more menstrual pain tended to experience orthodontic pain with greater intensity and for longer periods. Finally, menstrual cycle characteristics (length of cycle, duration, or amount of bleeding), were not influenced in the long term by the application of orthodontic forces. Until additional scientific knowledge becomes available, orthodontists should consider the possibility that female patients respond differently during the various stages of the menstrual cycle, as well as the potential repercussions. Regarding the effect of applying forces at different stages of the menstrual cycle, it was shown that when force is applied during the menstrual period teeth move faster (87). At this stage, estrogen and progesterone levels are lower (1). Estrogens are known bone resorption inhibitors and help to maintain bone mass (92). Previous research has shown that the rate of tooth movement is closely related to the activity of osteoclasts (93). Previous research has found a link between the rate of tooth displacement and the activity of osteoclasts (93) and estrogen can inhibit it (51). Furthermore, the reconstruction of periodontal tissue during tooth movement also involves the reconstruction of periodontal fibers; and estrogen can affect the deposition and cross-linking of collagen fibers (85). Progesterone has also been linked to bone preservation, either directly through its action on osteoblasts or indirectly through its influence on

glucocorticoid receptors and metalloproteinases (67) It's also been connected to a slower pace of tooth movement (94). Osteocalcin is marker of bone formation (95).

A previous systematic review on animal studies concluded that tooth movement was increased in the stages of the estrus cycle where the estrogen and/or progesterone levels were lower (22). The rate of movement after orthodontic forces was higher in the estrus group in two investigations on rats, when estrogen and progesterone levels are supposed to be at their lowest. In contrast, it was lower in proestrus animals, when estradiol levels are meant to be at their highest (83, 96). Estradiol levels varied as expected depending on the stage of the estrous cycle, with a peak in proestrus and the lowest concentration in estrus (83, 96). Estradiol levels were inversely related to the rate of tooth movement (83). There were also negative correlations between estradiol and serum TRAP activity, as well as pyridinoline, both of which are markers of bone resorption (83).The fluctuating pattern of serum progesterone differed from that of estradiol, with the peak occurring in diestrus. The lowest levels, like estradiol, were measured during estrus (83). Serum osteocalcin, a bone development marker, had a substantial relationship with progesterone (83).

Celebi et al. (85) who experimented on cats found that the estrus group had slower tooth movement, however this period in cats is marked by elevated estrogen levels. Exogenous administration of equine chorionic gonadotropin induced folliculogenesis and estrus in this group (eCG) (97). The concentrations of PGE2 and IL-1b were significantly higher in anestrus animals, which had the fastest tooth movement rate.

From the studies investigating the overall theme of pain during orthodontic treatment, it was shown that pain levels are higher in patients in the luteal phase than those in the follicular phase of the cycle (3, 90), when estrogen and progesterone levels are lower (1). The effects of female sex hormones on pain have been documented (12, 13, 98).

Ring et al. (99) and Ahmed et al. (14) have shown that pain is lower when estrogen levels are lower. However, others have shown opposite results (15, 100). Pain perception might be influenced by other parameters as well. Anxiety and quality of life have been shown to alter patients' perceptions of orthodontic discomfort (87, 101). Pain perception during dental treatment procedures may get affected by patients' anxiety (102, 103). Education levels are negatively connected with patients' first-day orthodontic pain levels, indicating that patients with higher educational levels may perceive less pain (104).

According to Ye et al. (88), females with severe primary dysmenorrhea tend to feel a persistent orthodontic pain, suggesting that dysmenorrhea could potentially serve as a reference to preliminarily predict orthodontic pain in females. Pain prediction for females could be important for medical and social reasons, but existing approaches are not practical enough for general application in clinical settings. Orthodontic pain and dysmenorrhea share common biomolecular pathways. Calcitonin gene-related peptide increases the feeling of pain perception by favoring the release of substance P, (105), induces orthodontic pain (106, 107)) and is highly expressed in patients with dysmenorrhea (108). Moreover, orthodontic pain and dysmenorrhea present common temporal characteristics on a near monthly basis and peak at the beginning

Duan et al. (89) showed that at the beginning fixed orthodontic therapy may lead to elongation the first month menstrual cycle, but not subsequently. Other characteristics like the duration or amount of bleeding where not shown to be affected. The influence of fixed orthodontic treatment on menstrual cycle length in not yet clear although majority of previous studies have revealed negative effect of stress and psychological factors on the menstrual cycle (109).

Even from this limited set of data, one could understand that it would be useful for the

orthodontist not to ignore the fact that menstruating patients could exhibit differential physiological bone remodeling in different menstrual cycle stages, as well as the possible clinical implications. In terms of mechanotherapy, it is important to remember that patients may require more anchorage preparation if force is applied during the phases when estrogen levels are lowest. On the contrary, activation during these stages may promote tooth movement, thereby shortening the total duration of orthodontic treatment. Fixed appliances should be removed during periods when high amounts of estrogen or progesterone are circulating, however this is not explicitly studied in the material collected. Finally, the phase of the cycle influences significantly how females perceive orthodontic pain, and the severity of menstrual pain can be a marker of pain associated with orthodontic forces.

### 6.2. Strengths and limitations of the present review

The adoption of a well-established technique is one of the review's strengths. The data retrieval approach used for electronic and manual sources was complete and comprehensive, with no pre-set constraints on language, publication date, or status. In order to avoid potential biases, screening, eligibility verification, information abstraction, and bias risk assessment were all done twice, and any disagreements were resolved through conversation until a final agreement was reached. The current evaluation has some limitations, which stem mostly from the nature and characteristics of the studies included in it, as well as the data gathered during the review process. Furthermore, the employment of specific modes to elicit orthodontic tooth movement limits the applicability of the acquired data to real clinical situations.

### 6.3. Recommendations for future research

Because female patients make up the majority of orthodontic patients, more well-designed experimental studies to examine and understand the effect of the menstrual

cycle on orthodontic tooth movement could be useful to clinicians. Standardization of study designs is highly desirable (110). Furthermore, future research should simulate, as closely as possible, scenarios in clinical practice in humans in terms of force magnitude as well as the characteristics of the force delivery method used.

## 7. CONCLUSION

Menstrual cycle presents interrelationship with the phenomena associated with orthodontic tooth movement and the orthodontist should consider the possible implications.

# 8. REFERENCES


1.Proffit WR, Fields HW, Larson B, Sarver DM. Contemporary orthodontics-e-book: Elsevier Health Sciences; 2018.
2.Zhang M, McGrath C, Hägg U. Changes in oral health-related quality of life during fixed orthodontic appliance therapy. American Journal of Orthodontics and Dentofacial Orthopedics. 2008;133(1):25-9.
3.Long H, Zhou Y, Pyakurel U, Liao L, Jian F, Xue J, et al. Comparison of adverse effects between lingual and labial orthodontic treatment: a systematic review. The Angle Orthodontist. 2013;83(6):1066-73.
4.De Oliveira C, Sheiham A. Orthodontic treatment and its impact on oral health-related quality of life in Brazilian adolescents. Journal of orthodontics. 2004;31(1):20-7.
5.Krukemeyer AM, Arruda AO, Inglehart MR. Pain and orthodontic treatment: patient experiences and provider assessments. The Angle Orthodontist. 2009;79(6):1175-81.
6.Scheurer PA, Firestone AR, Bürgin WB. Perception of pain as a result of orthodontic treatment with fixed appliances. The European Journal of Orthodontics. 1996;18(1):349-57.
7.Bergius M, Berggren U, Kiliaridis S. Experience of pain during an orthodontic procedure. European journal of oral sciences. 2002;110(2):92-8.
8.Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1(3):277-99.
9.Graber TM, Eliades T, Athanasiou AE. Risk management in orthodontics: experts' guide to malpractice. 2004.
10.Castelo-Branco C, Reina F, Montivero AD, Colodrón M, Vanrell JA. Influence of high-intensity training and of dietetic and anthropometric factors on menstrual cycle disorders in ballet dancers. Gynecological endocrinology. 2006;22(1):31-5.
11.Lawson CC, Whelan EA, Hibert ENL, Spiegelman D, Schernhammer ES, Rich-Edwards JW. Rotating shift work and menstrual cycle characteristics. Epidemiology (Cambridge, Mass). 2011;22(3):305.
12.Berger M, Szalewski L, Bakalczuk M, Bakalczuk G, Bakalczuk S, Szkutnik J. Association between estrogen levels and temporomandibular disorders: a systematic literature review. Przeglad menopauzalny= Menopause review. 2015;14(4):260.
13.Frölich MA, Banks C, Warren W, Robbins M, Ness T. The association between progesterone, estradiol, and oxytocin and heat pain measures in pregnancy: An observational cohort study. Anesthesia & Analgesia. 2016;123(2):396-401.
14.Ahmed A, Khan F, Ali M, Haqnawaz F, Hussain A, Azam S. Effect of the menstrual cycle phase on post-operative pain perception and analgesic requirements. Acta anaesthesiologica scandinavica. 2012;56(5):629-35.
15.Arab M, Mirkheshti A, Noghabaei G, Ashori A, Ghasemi T, Hosseini-Zijoud SM. The effect of premenstrual syndrome and menstrual phase on postoperative pain. Anesthesiology and pain medicine. 2015;5(2).
16.Teepker M, Peters M, Vedder H, Schepelmann K, Lautenbacher S. Menstrual variation in experimental pain: correlation with gonadal hormones. Neuropsychobiology. 2010;61(3):131-40.
17.Jacob S, Spencer NA, Bullivant SB, Sellergren SA, Mennella JA, McClintock MK. Effects of breastfeeding chemosignals on the human menstrual cycle. Human Reproduction. 2004;19(2):422-9.
18.Morishita M, Shimazu A, Iwamoto Y. Analysis of oestrogen receptor mRNA by reverse transcriptase-polymerase chain reaction in human periodontal ligament cells. Archives of oral biology. 1999;44(9):781-3.

19.Jiang L, Tang Z. Expression and regulation of the ERK1/2 and p38 MAPK signaling pathways in periodontal tissue remodeling of orthodontic tooth movement. Molecular medicine reports. 2018;17(1):1499-506.
20.Fang W, David T, Xing L, LASSILA LV, NAGAS E, VALLITTU PK, et al. Dental Research. 2012.
21.Khosla S, Melton III LJ, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? Journal of Bone and Mineral Research. 2011;26(3):441-51.
22.Almidfa NSS, Athanasiou AE, Makrygiannakis MA, Kaklamanos EG. Does the rate of orthodontic tooth movement change during the estrus cycle? A systematic review based on animal studies. BMC oral health. 2021;21(1):1-9.
23.Maleeh I, Robinson J, Wadhwa S. Role of alveolar bone in mediating orthodontic tooth movement and relapse. Biology of Orthodontic Tooth Movement: Springer; 2016. p. 1-12.
24.Kashyap S. Current concepts in the biology of orthodontic tooth movement: a brief overview. NJDSR. 2016;1(4):28-31.
25.Alansari S, Sangsuwon C, Vongthongleur T, Kwal R, chneh Teo M, Lee YB, et al., editors. Biological principles behind accelerated tooth movement. Seminars in Orthodontics; 2015: Elsevier.
26.Roberts SC, Havlicek J, Flegr J, Hruskova M, Little AC, Jones BC, et al. Female facial attractiveness increases during the fertile phase of the menstrual cycle. Proceedings of the Royal Society of London Series B: Biological Sciences. 2004;271(suppl_5):S270-S2.
27.Ferguson DJ, Wilcko MT. Tooth movement mechanobiology: toward a unifying concept. Biology of Orthodontic Tooth Movement: Springer; 2016. p. 13-44.
28.Schwarz AM. Tissue changes incidental to orthodontic tooth movement. International Journal of Orthodontia, Oral Surgery and Radiography. 1932;18(4):331-52.
29.Farrar JN. A Treatise on the Irregularities of the Teeth and Their Correction: Including, with the Author's Practice, Other Current Methods: De Vinne Press; 1888.
30.Asiry MA. Biological aspects of orthodontic tooth movement: A review of literature. Saudi journal of biological sciences. 2018;25(6):1027-32.
31.Alikhani M, Alansari S, Sangsuwon C, Nervina J, Teixeira C. Biphasic theory of tooth movement: cytokine expression and rate of tooth movement. Biology of orthodontic tooth movement: Springer; 2016. p. 45-65.
32.Mostafa YA, Weaks-Dybvig M, Osdoby P. Orchestration of tooth movement. American journal of orthodontics. 1983;83(3):245-50.
33.Hadjidakis DJ, Androulakis II. Bone remodeling. Annals of the New York Academy of Sciences. 2006;1092(1):385-96.
34.de Kretser D, Loveland K, O'Bryan M. Spermatogenesis, in, Jameson JL and DeGroot LJ, Endocrinology: Adult and Pediatric. Elsevier. 2015;36:2325-53.
35.Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. Journal of Bone and Mineral Research. 2000;15(11):2245-50.
36.Wastney M, Martin B, Peacock M, Smith D, Jiang X-Y, Jackman L, et al. Changes in calcium kinetics in adolescent girls induced by high calcium intake. The journal of clinical endocrinology & metabolism. 2000;85(12):4470-5.
37.Schiessl H, Frost H, Jee W. Estrogen and bone-muscle strength and mass relationships. Bone. 1998;22(1):1-6.

38.Lyritis G, Schoenau E, Skarantavos G. Osteopenic syndromes in the adolescent female. Annals of the New York Academy of Sciences. 2000;900(1):403-8.
39.Schoenau E, Neu C, Rauch F, Manz F. The development of bone strength at the proximal radius during childhood and adolescence. The Journal of Clinical Endocrinology & Metabolism. 2001;86(2):613-8.
40.Bartzela T, Türp JC, Motschall E, Maltha JC. Medication effects on the rate of orthodontic tooth movement: a systematic literature review. American Journal of Orthodontics and Dentofacial Orthopedics. 2009;135(1):16-26.
41.Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. New England Journal of Medicine. 2002;346(5):340-52.
42.Jensen E, Jacobson H, Smith S, Jungblut P, De Sombre E. The use of estrogen antagonists in hormone receptor studies. Gynecologic and Obstetric Investigation. 1972;3(1-4):108-23.
43.Ray S, Rastogi R, Kumar A. Current status of estrogen receptors. Progress in drug research. 2002:201-32.
44.Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. Current genomics. 2006;7(8):497-508.
45.Conneely OM. Perspective: female steroid hormone action. Endocrinology. 2001;142(6):2194-9.
46.Windahl SH, Andersson G, Gustafsson J-Å. Elucidation of estrogen receptor function in bone with the use of mouse models. Trends in Endocrinology & Metabolism. 2002;13(5):195-200.
47.Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsberg TC, et al. Evidence of estrogen receptors in normal human osteoblast-like cells. Science. 1988;241(4861):84-6.
48.Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igarashi K, et al. Estrogen prevents bone loss via estrogen receptor α and induction of Fas ligand in osteoclasts. Cell. 2007;130(5):811-23.
49.Srivastava S, Toraldo G, Weitzmann MN, Cenci S, Ross FP, Pacifici R. Estrogen decreases osteoclast formation by down-regulating receptor activator of NF-κB ligand (RANKL)-induced JNK activation. Journal of Biological Chemistry. 2001;276(12):8836-40.
50.Turner RT, Colvard DS, Spelsberg TC. Estrogen inhibition of periosteal bone formation in rat long bones: down-regulation of gene expression for bone matrix proteins. Endocrinology. 1990;127(3):1346-51.
51.Syed F, Khosla S. Mechanisms of sex steroid effects on bone. Biochemical and biophysical research communications. 2005;328(3):688-96.
52.Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. The Journal of clinical investigation. 2006;116(5):1186-94.
53.Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor κB ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocrine reviews. 2008;29(2):155-92.
54.Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. Clinical therapeutics. 2015;37(8):1837-50.
55.Pacifici R. Estrogen deficiency, T cells and bone loss. Cellular immunology. 2008;252(1-2):68-80.
56.Xu Y, Chu N, Qiu X, Gober H-J, Li D, Wang L. The interconnected role of chemokines and estrogen in bone metabolism. Bioscience trends. 2016;10(6):433-44.

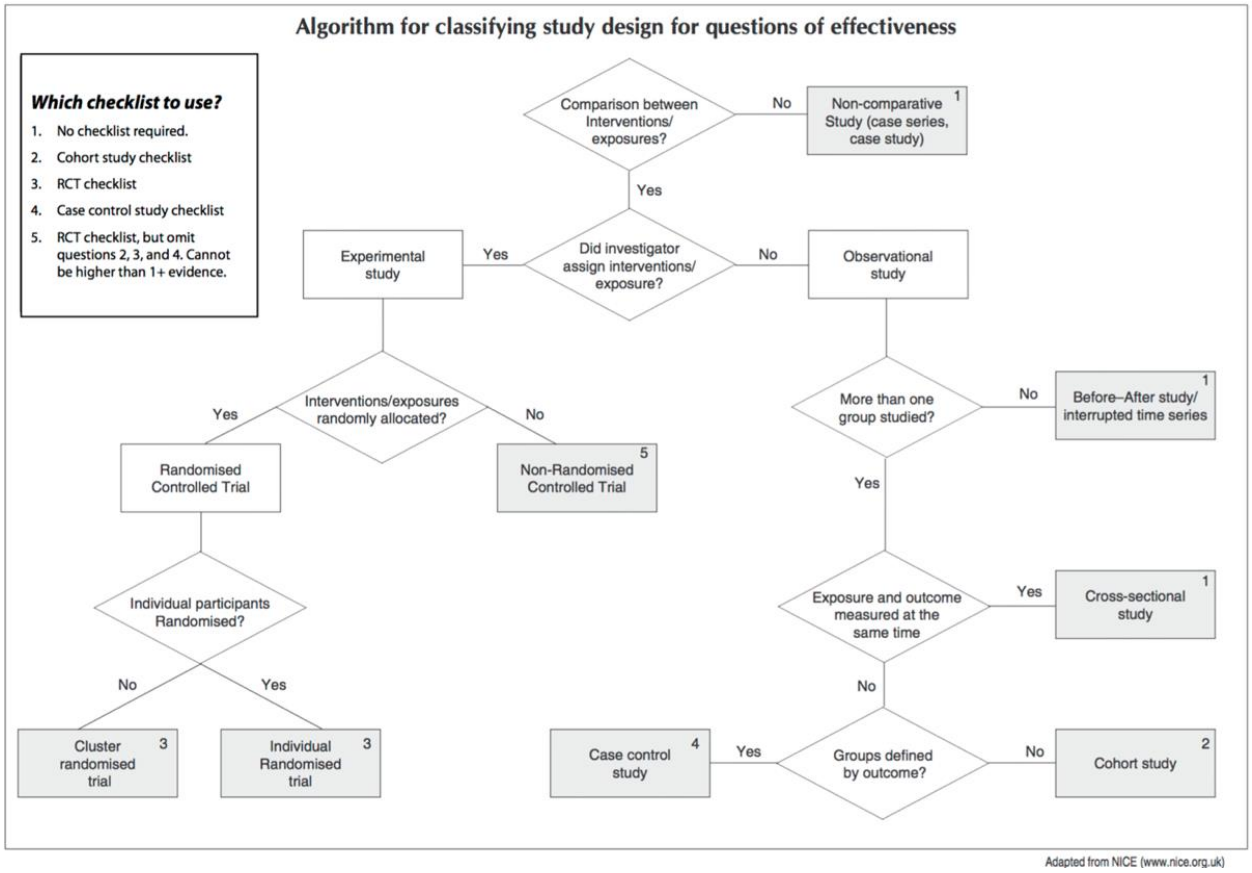
57.Määttä JA, Büki KG, Gu G, Alanne MH, Vääräniemi J, Liljenbäck H, et al. Inactivation of estrogen receptor α in bone-forming cells induces bone loss in female mice. The FASEB Journal. 2013;27(2):478-88.
58.Kondoh S, Inoue K, Igarashi K, Sugizaki H, Shirode-Fukuda Y, Inoue E, et al. Estrogen receptor α in osteocytes regulates trabecular bone formation in female mice. Bone. 2014;60:68-77.
59.Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, et al. Estrogens and androgens in skeletal physiology and pathophysiology. Physiological reviews. 2017;97(1):135-87.
60.Macari S, Duffles LF, Queiroz-Junior CM, Madeira MF, Dias GJ, Teixeira MM, et al. Oestrogen regulates bone resorption and cytokine production in the maxillae of female mice. Archives of oral biology. 2015;60(2):333-41.
61.Wronski T, Dann L, Scott K, Cintron M. Long-term effects of ovariectomy and aging on the rat skeleton. Calcified tissue international. 1989;45(6):360-6.
62.Kubo T, Shiga T, Hashimoto J, Yoshioka M, Honjo H, Urabe M, et al. Osteoporosis influences the late period of fracture healing in a rat model prepared by ovariectomy and low calcium diet. The Journal of steroid biochemistry and molecular biology. 1999;68(5-6):197-202.
63.Horowitz MC. Cytokines and estrogen in bone: anti-osteoporotic effects. Science. 1993;260(5108):626-7.
64.Tanaka M, Ejiri S, Toyooka E, Kohno S, Ozawa H. Effects of ovariectomy on trabecular structures of rat alveolar bone. Journal of periodontal research. 2002;37(2):161-5.
65.Jeffcoat M. The association between osteoporosis and oral bone loss. Journal of periodontology. 2005;76:2125-32.
66.Isobe N, Keshavan A, Gourraud P-A, Zhu AH, Datta E, Schlaeger R, et al. Association of HLA genetic risk burden with disease phenotypes in multiple sclerosis. JAMA neurology. 2016;73(7):795-802.
67.Graham JD, Clarke CL. Physiological action of progesterone in target tissues. Endocrine reviews. 1997;18(4):502-19.
68.Wei LL, Leach MW, Miner RS, Demers LM. Evidence for progesterone receptors in human osteoblast-like cells. Biochemical and biophysical research communications. 1993;195(2):525-32.
69.Prior J. Progesterone as a bone-trophic hormone. Endocrine Reviews. 1990;11(2):386-98.
70.Singh AK, Chattopadhyay R, Chakravarty B, Chaudhury K. Altered circulating levels of matrix metalloproteinases 2 and 9 and their inhibitors and effect of progesterone supplementation in women with endometriosis undergoing in vitro fertilization. Fertility and sterility. 2013;100(1):127-34. e1.
71.Allen TK, Feng L, Grotegut CA, Murtha AP. Progesterone receptor membrane component 1 as the mediator of the inhibitory effect of progestins on cytokine-induced matrix metalloproteinase 9 activity in vitro. Reproductive sciences. 2014;21(2):260-8.
72.Plant TM, Zeleznik AJ. Knobil and Neill's physiology of reproduction: Academic Press; 2014.
73.Xu X, Zhao Q, Yang S, Fu G, Chen Y. A new approach to accelerate orthodontic tooth movement in women: Orthodontic force application after ovulation. Medical hypotheses. 2010;75(4):405-7.
74.Melsen B. Potential adult orthodontic patients–who are they? Adult orthodontics. 2012:1-11.

75.Baumrind S, Curry S. American Association of Orthodontists Foundation Craniofacial Growth Legacy Collection: Overview of a powerful tool for orthodontic research and teaching. American Journal of Orthodontics and Dentofacial Orthopedics. 2015;148(2):217-25.
76.Jiang N, Guo W, Chen M, Zheng Y, Zhou J, Kim SG, et al. Periodontal ligament and alveolar bone in health and adaptation: tooth movement. Tooth Movement. 2016;18:1-8.
77.Xiao W, Wang Y, Pacios S, Li S, Graves DT. Cellular and molecular aspects of bone remodeling. Tooth movement. 2016;18:9-16.
78.Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1-9.
79.Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.
80.Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10):e1-e34.
81.McGuinness LA, Higgins JP. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research synthesis methods. 2021;12(1):55-61.
82.Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. NewCastle–Ottawa quality assessment scale—case control studies. Belia Vida Centre, Namibia. 2017.
83.Haruyama N, Igarashi K, Saeki S, Otsuka-Isoya M, Shinoda H, Mitani H. Estrous-cycle-dependent variation in orthodontic tooth movement. Journal of dental research. 2002;81(6):406-10.
84.Tan Z, Zhao Q, Chen Y. The mutual effects between orthodontic tooth movement and estrous cycle or estrogen. Biological Rhythm Research. 2010;41(1):75-81.
85.Celebi AA, Demirer S, Catalbas B, Arikan S. Effect of ovarian activity on orthodontic tooth movement and gingival crevicular fluid levels of interleukin-1β and prostaglandin E2 in cats. The Angle Orthodontist. 2013;83(1):70-5.
86.Xi Y, Hongwei D, Bin W, Lan H. Preliminary study on the best-exerted force chance in the female menstrual cycle. West China Journal of Stomatology. 2014;32(3).
87.Bin W, Xi Y, Jian-ping Z, Gang F, Hong-wei D, Lan H. Orthodontic tooth movement at different stages of adolescent female menstrual cycle. Chinese Journal of Tissue Engineering Research. 2014;18(15):2332.
88.Ye R, Wang S, Li Y, Wu R, Pei J, Wang J, et al. Primary dysmenorrhea is potentially predictive for initial orthodontic pain in female patients. The Angle Orthodontist. 2014;84(3):424-9.
89.Duan P, Qu W, Zou S, Chen Y, Lan H, Farella M, et al. Influence of fixed orthodontic treatment on the menstrual cycle of adult females: A prospective longitudinal study. The Angle Orthodontist. 2016;86(3):475-80.
90.Ileri Z, Baka ZM, Akin M, Apiliogullari S, Basciftci FA. Effect of menstrual cycle on orthodontic pain perception. Journal of Orofacial Orthopedics/Fortschritte der Kieferorthopädie. 2016;77(3):168-75.
91.Zittermann A, Schwarz I, Scheld K, Sudhop T, Berthold H, Von Bergmann K, et al. Physiologic fluctuations of serum estradiol levels influence biochemical markers of bone resorption in young women. The Journal of Clinical Endocrinology & Metabolism. 2000;85(1):95-101.

92.Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends in Endocrinology & Metabolism. 2012;23(11):576-81.
93.Igarashi K, Mitani H, Adachi H, Shinoda H. Anchorage and retentive effects of a bisphosphonate (AHBuBP) on tooth movements in rats. American Journal of Orthodontics and Dentofacial Orthopedics. 1994;106(3):279-89.
94.Poosti M, Basafa M, Eslami N. Progesterone effects on experimental tooth movement in rabbits. Journal of the California Dental Association. 2009;37(7):483-6.
95.Komori T. Functions of osteocalcin in bone, pancreas, testis, and muscle. International journal of molecular sciences. 2020;21(20):7513.
96.Guo J, Che X, Zhao Q, Chen Y. An experimental study on the relationship between the orthodontic tooth movements and menstrual cycle. Shanghai kou Qiang yi xue= Shanghai Journal of Stomatology. 2007;16(2):187-91.
97.Pelican KM, Wildt DE, Pukazhenthi B, Howard J. Ovarian control for assisted reproduction in the domestic cat and wild felids. Theriogenology. 2006;66(1):37-48.
98.Wise EA, Riley III JL, Robinson ME. Clinical pain perception and hormone replacement therapy in postmenopausal women experiencing orofacial pain. The Clinical journal of pain. 2000;16(2):121-6.
99.Ring C, van Zanten JJV, Kavussanu M. Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. Biological Psychology. 2009;81(3):189-91.
100.de Kruijf M, Stolk L, Zillikens MC, de Rijke YB, Bierma-Zeinstra SM, Hofman A, et al. Lower sex hormone levels are associated with more chronic musculoskeletal pain in community-dwelling elderly women. Pain. 2016;157(7):1425-31.
101.Cioffi I, Michelotti A, Perrotta S, Chiodini P, Ohrbach R. Effect of somatosensory amplification and trait anxiety on experimentally induced orthodontic pain. European journal of oral sciences. 2016;124(2):127-34.
102.Sanikop S, Agrawal P, Patil S. Relationship between dental anxiety and pain perception during scaling. Journal of oral science. 2011;53(3):341-8.
103.Van Wijk A, Makkes P. Highly anxious dental patients report more pain during dental injections. British dental journal. 2008;205(3):E7-E.
104.Abu Alhaija ES, AlDaikki A, Al-Omairi MK, Al-Khateeb SN. The relationship between personality traits, pain perception and attitude toward orthodontic treatment. The Angle Orthodontist. 2010;80(6):1141-9.
105.McCulloch J, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: functional role in cerebrovascular regulation. Proceedings of the National Academy of Sciences. 1986;83(15):5731-5.
106.Hall M, Masella R, Meister M. PDL neuron-associated neurotransmitters in orthodontic tooth movement: identification and proposed mechanism of action. Today's FDA: official monthly journal of the Florida Dental Association. 2001;13(2):24-5.
107.Norevall LI, Forsgren S, Matsson L. Expression of neuropeptides (CGRP, substance P) during and after orthodontic tooth movement in the rat. The European Journal of Orthodontics. 1995;17(4):311-25.
108.Barcena de Arellano ML, Arnold J, Vercellino GF, Chiantera V, Ebert AD, Schneider A, et al. Influence of nerve growth factor in endometriosis-associated symptoms. Reproductive Sciences. 2011;18(12):1202-10.
109.Edozien LC. Mind over matter: psychological factors and the menstrual cycle. Current Opinion in Obstetrics and Gynecology. 2006;18(4):452-6.
110.Malfait A-M, Little CB. On the predictive utility of animal models of osteoarthritis. Arthritis research & therapy. 2015;17(1):1-14.

# 9. APPENDICES

**Appendix I.** Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness.



**Appendix II.** Strategy for database search.

| Database [2022 02 01] | Search strategy | Hits |
|---|---|---|
| **PubMed** | (estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption) | **12** |
| **Cochrane Central Register of Controlled Trials** | (estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption) in Title Abstract Keyword - (Word variations have been searched) | **3** |
| **Cochrane Database of Systematic Reviews** | (estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption) in Title Abstract Keyword - (Word variations have been searched) | **0** |
| **Scopus** | TITLE-ABS-KEY((estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)) | **12** |
| **Web of Science™** | TOPIC: ((estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption))<br>Timespan: All years. Databases: WOS, KJD, RSCI, SCIELO, ZOOREC.<br>Search language=Auto | **12** |
| **Arab World Research Source** | TI tooth movement OR AB tooth movement | **3** |
| **ProQuest Dissertations and Theses Global** | ti((estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)) OR ab((estrus OR oestrus OR estrus OR oestrus OR anestrus OR anoestrus OR anestrus OR anoestrus OR proestrus OR proestrus OR proestrus OR proestrus OR metestrus OR metoestrus OR metestrus OR metoestrus OR diestrus OR dioestrus OR diestrus OR dioestrus OR "ovarian cycle" OR ovulation OR "luteal phase" OR "uterine cycle" OR menstruation OR menses OR menstruating OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)) | **1** |