EFFECT OF ESTRUS CYCLE ON THE RATE OF ORTHODONTIC TOOTH MOVEMENT: A SYSTEMATIC REVIEW OF ANIMAL STUDIES

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ABSTRACT

Effect of estrus cycle on the rate of orthodontic tooth movement: A systematic review of animal studies

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Background: As estrogen levels affect bone metabolism, the hormonal changes encountered during the estrus cycle may exert an influence on the rate of orthodontic tooth movement.

Aim: To systematically investigate the available evidence from animal studies regarding the effect of estrus cycle on the rate of orthodontic tooth movement.

Materials and Methods: Search without restriction for published and unpublished literature and hand searching took place. Controlled studies investigating the effect of estrus cycle on the rate of orthodontic tooth movement were reviewed. Following study retrieval and selection, relevant data was extracted and the risk of bias was assessed using the SYRCLE's Risk of Bias Tool.

Results: From the final records, 3 studies met the inclusion criteria. The rate of orthodontic tooth movement was increased during the stages of the estrus cycle when estrogen and/or progesterone levels were lower. The risk of bias in the retrieved studies was assessed to be unclear.

Conclusion: Hormonal changes during the estrus cycle may affect the rate of orthodontic tooth movement. Although these animal experiment results should be approached cautiously, it could be safe practice to consider the possible impact of these physiological changes in the clinical setting until more information becomes available.

DEDICATION

This dissertation is dedicated to my favorite person my best friend my everything. Thank you for always being there making it all seem easy even when all hell was breaking loose.

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: Noura Saeed Sultan Almidfa

Signature:

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1. INTRODUCTION

The objective of orthodontic treatment is to provide a functional, stable and pleasing occlusion in harmony with overall facial esthetics (Proffit et al., 2019). Studies have shown that the majority of patients seeking orthodontic treatment are adolescent and adult females (Jacob et al., 2004).

In women the menstrual cycle is a series of events, characterized by periodic and repeated hormonal fluctuations that prepare the female body for a possible pregnancy (Zeleznik and Plant, 2015; Kasper et al., 2018). Estrogen levels are at baseline levels during menses, then slowly increase reaching its peak a day or two before ovulation. After ovulation estrogen levels drop, but during most of the luteal phase the production of estrogen is maintained at lower levels before decreasing some more and reach its lowest level during menstruation (Kasper et al., 2018). Progesterone is produced after ovulation during the luteal phase (Zeleznik and Plant, 2015; Pooley et al., 2018). Both estrogen and progesterone have been shown to affect bone turnover (Bartzela et al, 2009).

As orthodontic tooth movement is achieved by alterations in the balance between resorption and formation of the alveolar bone and it could potentially be modulated by any development affecting the pertinent cellular and bimolecular networks (Jiang et al., 2016; Xiao et al., 2016). For example, numerous studies have shown that estrogen deficiency increases the rate of tooth movement (Xu et al., 2010). As estrogen levels fluctuate monthly during the menstrual cycle, the bone remodeling process could be influenced periodically in adolescent and adult females undergoing orthodontic tooth movement (Zittermann et al., 2000).

Thus, understanding the impact of the menstrual cycle on orthodontic tooth movement and considering the possible effects could be of benefit to the clinician. As relevant

research in human subjects presents significant practical limitations, the use of animal models could prove to be beneficial (Lelovas et al., 2008; Komori et al., 2015). However, to the best of the authors' knowledge an evidence-based summary of the information regarding the possible effects on the amount of orthodontic tooth movement has not been compiled.

The aim of the present dissertation submitted to the Hamdan Bin Mohammed College of Dental Medicine of the Mohammed Bin Rashid University of Medicine and Health Sciences in partial fulfillment of the requirements for the Degree of Master of Science in Orthodontics was to systematically investigate and appraise the quality of the available evidence from animal studies regarding the effect of the estrus cycle phases on the rate of orthodontic tooth movement.

2. REVIEW OF THE LITERATURE

Orthodontic treatment is based on the principle that when mechanical loads are applied on teeth they provoke a spectrum of cellular responses that lead to bone adaptation in a new environment and consequently movement of the teeth (Maleeh et al., 2016). Clinicians have always wanted to understand the basic concepts of the mechanisms of tooth movement in order to decrease treatment duration and increase patient satisfaction (Kashyap, 2016).

2.1. Tooth movement and bone physiology

2.1.1. Orthodontic tooth movement

Orthodontic tooth movement is the result of various biological responses when external forces, intermittent or continuous, are applied on teeth (Proffit et al., 2019). These loads change the mechanical environment of the teeth and the surrounding tissues, causing the periodontal ligament to distort and the bone to bend (Kashyap et al., 2016). Numerous theories have been described in the literature with the attempt to explain the mechanisms involved in tooth movement associated with orthodontic treatment (Maleeh et al., 2016). In general, theories have been focusing on the fact that the bone and the periodontal ligament are the targets of the stimuli (Alansari et al., 2015). To some extent these postulations on orthodontic tooth movement remain theoretical but the histological documentation is undeniable (Roberts et al., 2004). Traditionally, the pressure tension theory that is based upon over a hundred years of observations, is the one embedded in clinicians' minds, in order to explain and predict tooth movement (Ferguson and Wilcko, 2016).

The original investigations, which form the basis of our current understanding of tooth movement, were carried out on dogs by the Swedish dentist Carl Sandstedt (1904). In

his landmark experiments, Sandstedt concluded that force application induced tissue changes to the surrounding periodontal ligament and alveolar bone. Subsequently, Oppenheim (1911) observed that when a tooth moves, a “pressure side” and a “tension side” are formed in the periodontal ligament.

Schwarz (1932) later hypothesized that orthodontic forces should not be “greater than the pressure in the capillary blood”. The alteration in blood flow results in a lower oxygen supply in the pressure side, due to the compression of periodontal fibers, and more oxygen to the tension side. The final histological result is the alveolar bone resorption observed on the pressure side and apposition of new bone on the tension side (Ferguson and Wilcko, 2016). In the case that the capillary blood pressure is exceeded, then compression can lead to tissue necrosis through suffocation of the strangulated periodontium (Schwarz, 1932). Reitan (1957) detected that after the application of even the lightest of forces, hyalinization might occur in the periodontal ligament. Additional hyalinization happened following force application when the tooth had shorter roots, which attributed to increased pressure development.

The bone bending theory explains that when an orthodontic appliance is activated, the forces delivered to the tooth are transmitted to the surrounding tissues (Farrar, 1888). These forces bend the bone, resulting in mechanical perturbation in the periodontal ligament and the osseous tissue. Bone has been found to be more elastic than the other tissues and to bend far more readily in response to force application (Baumrind, 1969). In order to account for the tooth movement over and above the width of the periodontal ligament, bone bending must occur. Moreover, when a force is applied on a given tooth, this tooth becomes displaced many times more than the periodontal ligament width (Roberts et al., 2004).

With the aid of this theory, investigators 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. This theory could also help in the interpretation of the faster tooth movement occurring in children, who have more flexible and less calcified bones than adults (Roberts et al., 2004).

Potential electrical signals generated after alveolar bone bending have been also implicated in orthodontic tooth movement phenomena (Proffit et al., 2019). In the 60's the interest in piezoelectricity as a stimulus for bone remodeling was immense. It was shown that distortion of crystalline structures generated small electrical charges, which could potentially be responsible for signaling the osseous changes associated with the mechanical force application. Animals who have been subjected to electromagnetic stimulation during orthodontic tooth movement demonstrate a faster rate of movement (Stark, 1987). Based on this assumption clinical attempts to accelerate the rate and amount of tooth movement by using pulsed magnetic fields have been carried out (Proffit et al., 2019).

2.1.2. Cell types in bone

Bone is a dynamic tissue that remodels in response to a mechanical force. The cells that accomplish this response are dispersed throughout the bone and each is specialized to perform specific functions needed to activate cells, resorb bone and deposit new bone matrix that fulfils the function of the skeleton (Alansari et al., 2015).

There are three main types of cells identified in the alveolar bone that respond to orthodontic stimuli namely osteoblasts, osteoclasts and osteocytes (Alikhani et al., 2016).

Osteoblasts are mononuclear, primarily bone forming cells found in the bone surface at bone apposition sites (Alansari et al., 2015). They secrete matrix of bone and type I collagen. In addition to this, osteoblasts respond directly to strain from orthodontic stimuli (Maleeh et al., 2016). Though osteoblasts play a crucial role in preserving the integrity of alveolar bone during tooth movement, they are not the cells that determine how quickly a tooth will move (Alansari et al., 2015).

Subsequently after the initial movement in the periodontal ligament space, the teeth can only move towards areas of resorbed bone. The role of the second type of osseous tissue cells, the osteoclasts, becomes paramount. Osteoclasts are specialized macrophages formed by a collection of monocytic precursors that become one giant multinucleated cell. In fact, the osteoclasts determine the rate of bone resorption and consequently the rate of tooth movement (Alansari et al., 2015).

The third type of cells, the osteocytes are mature osteoblasts embedded in osseous lacunae. These cells have proprioceptive and responsive properties (Maleeh et al., 2016). The specific role of osteocytes remains still undetermined to some extent, but they have been found to coordinate osteoblast and osteoclast activation (Alikhani et al., 2016).

A fourth cell type is the bone lining cell, which is involved in bone protection and maintenance of bone fluids. These cells may also be involved in the propagation of the activation signal that initiates bone resorption and bone remodeling. Finally, the osteoprogenitor cells are the stem cell population tasked with generating osteoblasts (Maleeh et al., 2016).

Bone soluble factors such as the Colony-Stimulating Factor (CSF), the Receptor Activator of Nuclear factor-Kappa B Ligand (RANKL), Osteoprotegerin (OPG) and Bone Morphogenic Proteins (BMPs) regulate osteoclast differentiation (Maleeh et al.,

2016). All are produced by osteocytes found in the alveolar bone and osteoblasts found in the periodontal ligament (PDL).

The CSF as well as RANKL and its receptor RANK promote the differentiation of osteoclasts. Especially RANKL is the key molecule involved in the maturation of osteoclasts. In bone, osteocytes are major producers of RANKL and cause an increase in osteoclastogenesis by releasing soluble RANKL. This promotes its interaction with osteoclast precursors to stimulate their differentiation and activation. Thus, the increase in orthodontic tooth movement-induced RANKL expression may result from osteocytes within alveolar bone. This may explain why tooth movement in mice in which the osteocytes are removed leads to decrease in osteoclastic bone resorption (Maleeh et al., 2016).

2.1.3. Bone remodeling cycle

During the course of life bone tissue preserves its integrity and reacts to changes by continuous turnover, a process called bone remodeling. In the case of orthodontic tooth movement, bone remodeling consists of loss of bone mass at the periodontal ligament pressure areas and bone apposition at the tension areas. This succession of events has formed the central theme of the pressure-tension hypothesis (Mostafa et al., 1983).

The bone remodeling cycle includes three phases: the resorption phase, during which osteoclasts initiate to resorb and digest old bone. The reversal phase, when mononuclear cells appear on the bone surface and the formation phase, when osteoblasts lay down a layer of new bone until the resorbed bone is completely replaced. The integrity of bone seems to be controlled by hormones and many other proteins. The bone remodeling cycle is under systemic and local regulation. The main systemic regulators contain thyroid hormones in which parathyroid hormone (PTH) is the most important regulator.

As well as other hormones such as calcitriol, glucocorticoids, growth hormones and sex hormones (Hadjidakis and Androulakis, 2006). As far as local regulation of bone remodeling is concerned, a large number of cytokines and growth factors that affect bone cell functions have been identified (Hadjidakis and Androulakis, 2006). Skeletal homeostasis is maintained as long as the balance between resorption and bone formation remains unchanged (Alikhani et al., 2016).

During remodeling the fractions of bone that are being renewed are called bone remodeling units (BRU) at any given time. The bone in an activated BRU is first digested by osteoclasts a process taking few weeks. Then the lost bone is replaced by osteoblastic bone formation taking up to 3-4 months for a packet. This explains the discrepancy where increased resorption even when accompanied by increased formation of bone can lead to overall bone loss, as is the case of menopause associated with estrogen deficiency (Jameson and De Groot., 2015).

The time both before and during puberty crucially determines bone mass. About 25% of calcium is deposited in the skeleton throughout the years of the growth spurt in adolescents (Bailey et al., 2000). Increased bone retention of calcium is associated with high calcium intake, increased dietary absorption via the intestine and decreased bone resorption (Wastney et al., 2000). The latter phenomenon has been attributed to the increase in estrogen levels (Schiessl et al., 1998; Lyritis et al., 2000). It seems that during the pubertal period, girls will acquire more skeletal mass than that required for their level of physical work. The excessive increase in estrogen levels during puberty has been stipulated to lower the remodeling threshold, resulting in less bone resorption, while acquirement of bone from modeling and longitudinal growth continues (Schiessl et al., 1998; Lyritis et al., 2000).

It has also been noted that males gain bone mostly on periosteal surfaces while females accumulate bone on endocortical surfaces during the pubertal phase (Schoenau et al., 2001). The bone added on the endocortical surfaces has less impact on bone strength compared to the one added to periosteal surfaces. Thus, it might be the case that during puberty, the human female skeleton acquires calcium in excess of its immediate needs as an adaptation mechanism for the needs of subsequent reproductive cycles rather than for structural reinforcement. This phenomenon appears to be a characteristic of all vertebrates, and not unique to mammals. Animal experimental studies on rats, (Bowman and Miller, 1999) and birds (Miller, 1992) demonstrated the accumulation of excess skeletal mass prior to the initiation of reproduction.

2.2. Hormones and their effect on bone

Some hormones, such as estrogens, thyroid hormones, calcitonin, etc. are vital regulators of calcium homeostasis. They control the expression and secretion of RANKL and OPG. RANKL is a cytosine secreted by bone marrow cells, osteoblasts, and osteocytes, and it plays an important role in osteoclast maturation and differentiation. As previously mentioned RANK is the receptor for RANKL on the osteoclast precursors and part of the RANK/RANKL/OPG signaling pathway. The binding of RANKL to RANK stimulates the osteoclast differentiation and consequently, it stimulates bone resorption (Bartzela et al., 2009).

2.2.1. Estrogens

Estrogens are steroids and the primary female sex hormones produced by the endocrine system, distributed in the local tissues and the blood stream. Estrogens can be found in three major naturally occurring forms estradiol E2, estrone E1 and estriol E3. Estradiol

being the most potent hormone, produced in the ovaries and responsible for the reproductive and sexual function (Gruber et al., 2002). In an adult woman, the most dominant estrogens are estradiol and estrone. While in a pregnant female the main estrogen is estradiol (Jensen et al., 1972; Ray et al., 2002; Marino et al., 2006). Estrogens induce significant changes to the female body during puberty, like the stimulation of growth and the development of the female sex organs. Moreover, they contribute to the growth of the mammary ducts and glands observed during the same period. Estrogens also affect bones as they regulate the osteoclastic activity and stimulate the osteoblastic activity, in such a way that they are essential to maintain adequate bone mineralization (Conneely 2001).

It is well recognized that estrogen levels play a critical role regarding bone mass preservation (Windahl et al., 2002). Estrogen receptors have been observed in human cells (Eriksen et al., 1988) and several lines of evidence support that inhibition of bone remodeling by estrogen is a result of osteoclastogenesis prevention from marrow precursors, as well as by induction of the Fas/FasL system that leads to osteoclast apoptosis (Srivastava et al., 2001; Nakamura et al., 2007). Estrogen exerts a further inhibitory role on bone resorption through effects on the receptor activator of nuclear factor-Kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system and the production of some pro-resorptive cytokines (e.g. IL-1, IL-6, IL-7, TNF) (Turner et al., 1990; Syed et al., 2005; Weitzmann et al., 2006; Kearns et al., 2008; Drake et al., 2015; Pacifici 2008; Xu et al., 2017). However, estrogen also affects directly the cells of the osteoblastic lineage contributing to bone preservation (Määttä et al., 2013; Kondoh et al., 2014).

During menopause, the decrease in estrogen levels is critical for the development of changes in the osseous tissues (Almeida et al., 2017). The osteoprotective effects of

estrogen are mediated through alpha receptors (ERα) in osteoblasts and osteoclasts (Macari et al., 2015). Deletion of osteoclast ERα leads to an increase in osteoclast proliferation and survival resulting in osseous loss (Nakamura et al., 2007). Regarding bone deposition, activation of the osteoblasts ERα enhances bone mineral density, by up regulating of OPG and Interleukin-6 (Ikeda et al., 2011). Deleterious effects of the lack of estrogens on the quality of newly formed bone have also been observed (Wronski et al., 1989; Kubo et al., 1999). Estrogen deficiency might affect the levels of important proteins, such as osteogenin and bone morphogenic proteins, causing a disruption of bone matrix formation and affecting the early stages of bone formation (Wronski et al., 1989). Histomorphometric data have also shown a reduction in osteoblast counts and further negative effects on the later stages of bone formation (Kubo et al., 1999). Thus, lack of estrogens will increase osteoclastogenesis and bone resorption, as well as affect adversely the volume of trabecular bone and the number of trabeculae in the alveolar processes, resulting in faster tooth movement (Horowitz, 1993; Tanaka et al., 2002; Jeffcoat, 2005).

Estrogen levels fluctuate during the menstrual cycle, it is the lowest during menses, then slowly increases during the follicular phase reaching its peak a day or two before ovulation. After ovulation estrogen levels drop, but during most of the luteal phase the production of estrogen is maintained at lower levels before decreasing some more and reach the lowest during menstruation (Kasper et al., 2018).

2.2.2. Progesterone

Progesterone is also a steroid sex hormone. It is responsible for the progestational changes of the endometrium. Progesterone stimulates the development of the breasts, exhibiting an action that is complementary to that of the estrogens. Progesterone is also

thermogenic meaning that it contributes to the increase in the basal temperature experienced by some women after ovulation by around 0.5 degree (Pooley et al., 2018). Progesterone has also been shown to exert bone protective effects (Graham et al., 1997). These results seem to be moderated directly via progesterone receptors in osteoblasts (Wei et al., 1993), as well as indirectly by acting as a ligand to the glucocorticoid receptor (Prior et al., 1990; Graham et al., 1997). Furthermore, progesterone may participate in the regulation of bone matrix, through its inhibitory action on metalloproteinase (Singh et al., 2013; Allen et al., 2014).

2.3. Menstrual cycle

The menstrual cycle corresponds to characteristic changes taking place in the ovaries' follicles the ovarian cycle and the physiological cycle of orderly sloughing of the endometrial lining of the uterus, the uterine cycle. Both cycles can be divided into three phases. The ovarian cycle is divided in the follicular phase, ovulation, and the luteal phase, whereas the uterine cycle is divided to menstruation, proliferative phase, and the secretory phase (Zeleznik and Plant, 2015; Kasper et al., 2018).

The length of the menstrual cycle is the number of days between the first day of menses (bleeding) to the beginning of the next cycle menses. Most cycles last between 25-30 days (Kasper et al., 2018).

2.3.1. Phases of the ovarian cycle

The ovarian menstrual cycle consists of two distinct phases separated by ovulation (Figure 1). The follicular phase starts on the first day of menses until ovulation. The stage after ovulation and up until the next menstruation is the luteal phase (Zeleznik and Plant., 2015; Pooley at al., 2018).

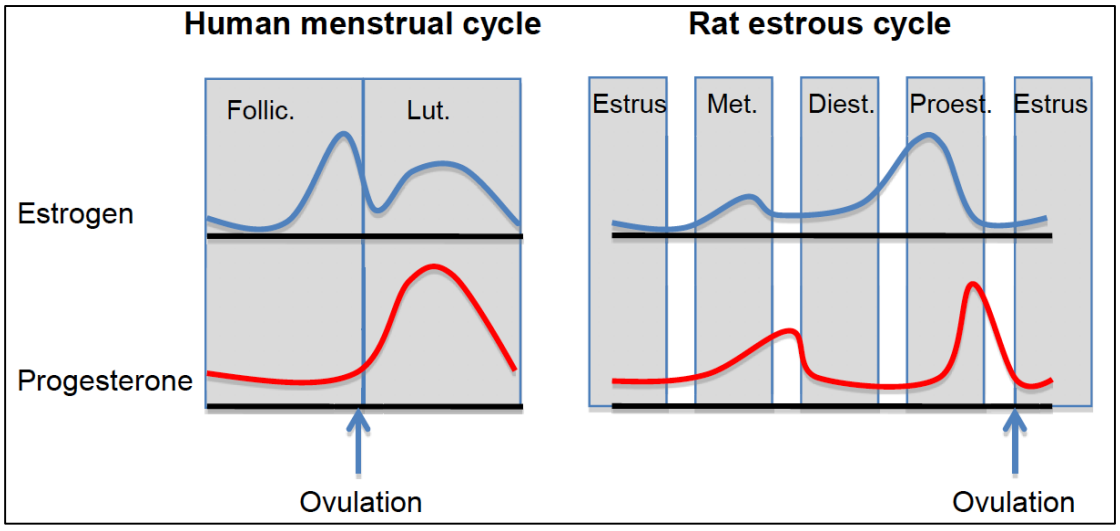

Figure 1. The human menstrual cycle and the rat estrus cycle [from Lebron-Milad and Milad, 2018).

The follicular phase starts at day one of the menstruation during which the body is preparing the oocytes for a possible pregnancy. The Follicle Stimulating Hormone (FSH) levels increase and stimulate the oocytes. Those oocytes are covered in a sac called follicle that gives the name to this phase. The Follicle Stimulating Hormone also stimulates the follicles to produce estradiol, which suppresses the release of the Luteinizing Hormone (LH) from the anterior pituitary gland. Between days 5 and 7 of the menstrual cycle, the follicular selection occurs, to allow only one follicle to ovulate and the rest to experience atresia. The follicular phase is divided into early, middle and late. Early follicular phase lasts from the first day of menstruation until the 4th, followed by the middle phase from day 5 to day 7, and the late phase from the 8th up until the 12th day. At the late phase the level of estrogen is at its highest (Zeleznik and Plant, 2015; Kasper et al., 2018).

During the next phase of the ovarian cycle, the phase of ovulation, the mature oocyte is released from the ovarian follicles into the oviduct. At this stage of the ovarian cycle,

estradiol levels attain a certain threshold above which the LH suppressing effect observed during the follicular phase is reversed, resulting in a LH surge by the production of a large quantity of LH. When the oocyte has nearly matured, levels of estradiol reach a threshold above which this effect is reversed and estrogen stimulates the production of a large amount of LH. The LH surges results in the maturation of the oocyte and the weakening of the wall of the follicle in the ovary, leading to the release of the secondary oocyte by the fully developed follicle (Zeleznik and Plant, 2015; Kasper et al., 2018).

The luteal phase gets the name because of the fact that the follicular cavity is transformed into a corpus luteum and keeps producing estrogen and significant amounts of progesterone. Interestingly in this phase, the average total body temperature of women is constantly 0.5°C higher than in the follicular phase (Zeleznik and Plant, 2015; Pooley et al., 2018).

2.3.2. Phases of the uterine cycle

The uterine cycle is divided into three phases: menstruation, proliferative phase, and the secretory phase (Kasper et al., 2018).

Menstruation is when menstrual bleeding or period or menses occur because of the sloughing of the endometrial lining of the uterus. It usually lasts on average 5 days and during this period both estrogen and progesterone levels are low. The average blood loss during menses is 35 ml, with a range of 10 to 80ml considered to be within normal limits (Kasper et al., 2018).

The proliferative phase is the second phase of the uterine cycle when the rise in the estrogen levels cause the endometrial lining of the uterus to proliferate. As the maturation of the ovarian follicles proceed, the levels of estradiol rise and initiate the

formation of the proliferative endometrium. Estradiol also stimulates the cervical crypts to produce mucus, which causes vaginal discharge (Kasper et al., 2018).

The final phase of the uterine cycle is the secretory phase and is correspondent to the luteal phase of the ovarian cycle. During this stage, the corpus luteum produces progesterone, which is important to prepare the endometrium for blastocyst implantation. Progesterone is also important for the very early stages of pregnancy, as it leads to the increase of the flow of blood in the uterus, the increase of uterine secretions and the reduction in smooth muscle contractile activity. As already mentioned, it results to an increase of a female's basal body temperature by 0.5°C higher than in the previous phases (Pooley et al., 2018).

2.4. Animals in human reproduction research

Laboratory animals have been playing an important role in research for years (Rand, 2008). During the course of history, ethical and practical considerations as well as social bans have prevented experimental studies of human subjects (Hau, 2008).

Rats have been one of the most commonly used animals for research. They are readily available, easy to handle and most importantly have comparable physiology and genetics to humans. The rat is the primary model for extensive studies of human reproduction research (Xu et al., 2010).

A complete understanding of the rat reproductive cycle is of utmost importance for these areas of scientific investigation (Xu et al., 2010). Cats also have been used in human reproduction research (Wildt et al., 1998).

2.4.1. Estrus cycle in rats

The term estrus was first used to describe the mammal sexual season (Michelle et al.,

2015). The estrus cycle of rats is comparable to human menstrual cycle; not only is the maintenance mechanism of the periodic rhythm similar in both cycles, but also the control of estrogen levels (Figure 1) (Levine, 2015).

The rat estrus cycle lasts 4 to 5 days. A dynamic process of different cell types that appear and recede in waves during the cycle takes place, corresponding to the changes in the levels of estradiol and progesterone secreted by the ovarian follicle (Levine, 2015).

The estrus cycle consists of the following four stages, proestrus, estrous, diestrus 1 (or metestrus) and diestrus 2 (diestrus) (Becker et al. 2005), which names come from the base word estrus that was first mentioned in 1900 Heape's publication (Heape, 1900). Estrus was derived to modern English through the Latin word estrus that originated from the Greek οἶστρος. Literally, it means horsefly and it refers to the fly that goddess Hera in Ancient Greek mythology sent to torment Io, one of Zeus's lovers. Later the word came to describe madness (Heape, 1900). This term was used by Heape (1900) to describe the "special period of sexual desire of the female" animal. In order to verify the accurate stage of the estrus cycle, vaginal smears are usually examined at specific times during the day in order to investigate the different cell populations (Becker et al., 2005; Levine, 2015).

Although, traditionally the estrus cycle is described to start from proestrus, recent descriptions start from diestrus 1 (or metestrus) and diestrus 2 (diestrus), which correspond to the follicular phase of the menstrual cycle (Becker et al. 2005).

The ovarian estrus cycle begins with a follicular phase, which is characterized by the development of follicles from oocytes in the rat ovary and is stimulated by low concentrations of FSH that are secreted from the pituitary. Moreover, during this period a gradual increase of estradiol levels is observed. This phase lasts around 2 days, the

first day called diestrus 1 or metestrus, and the second day is diestrus 2 or just diestrus. Metestrus is also characterized by the activity of the corpus luteum, which produces progesterone and is cytologically characterized by nucleated and cornified cells, whereas diestrus cells consist mainly of leukocytes (Becker et al., 2005; Levine, 2015; Lohmiller et al., 2020).

During proestrus, which in corresponds to pre-ovulatory period, estradiol increases dramatically, triggers GnRH release and induces a surge of LH from the pituitary that induces ovulation. Progesterone rises a few hours before ovulation and contributes to this process. Once LH and progesterone are released into the circulation, ovulation occurs 10–12 h later. At the stage of proestrus vaginal cytology shows a large number of non-cornified nucleated epithelial cells (Becker et al., 2005; Levine, 2015).

Estrus refers to the stage when the female is sexually receptive and corresponds to the actual day of ovulation. It comes after the LH surge and ovulation, and during this period estradiol and progesterone come to baseline levels. The estrus phase lasts usually 25-27 hours and cytological examination reveals 75% nucleated cells and 25% cornified cells (Becker et al., 2005; Levine, 2015).

2.4.2. Estrus cycle in cats

The estrus cycle in cats consists also of four phases of the estrus cycle: proestrus, estrus, diestrus and anestrus (or interestrus) (Wildt et al., 1998; Brown, 2011).

Proestrus, the time when the female cat (the queen) is attractive but not receptive, usually lasts less than 24 hours, and is associated with the presence of ovarian follicles and the increase in the levels of circulating estrogens and sometimes is not observed.

The following stage of estrus, when the queen is receptive, is characterized by the advanced development of the follicles and the maximum concentrations of estradiol.

Multiple copulations that may happen over multiple days, are thought to be necessary in most felids to stimulate the release of gonadotropin-releasing hormone (GnRH) and subsequent the LH surge, resulting in ovulation after mating. Estrus lasts 3 to 16 days (average 12) and its length is not affected by copulation or ovulation.

In case ovulation happens, the cycle enters the diestrus phase, when one or more corpora lutea produce progesterone that stays elevated for varying lengths of time regardless of whether conception occurs or not (Wildt et al., 1998; Brown, 2011).

After diestrus or if ovulation does not occur, the cat enters the anestrus (or interestrus) period, and the cycle repeats over and over between phases of follicular development. During the anestrus period the circulating estrogens are at their lowest levels (Wildt et al., 1998; Brown, 2011). Folliculogenesis and estrus can be initiated by exogenous hormones like porcine follicle stimulating hormone (pFSH) and equine chorionic gonadotropin (eCG) (Pelican et al., 2006).

2.5. Hormonal fluctuations during the menstrual cycle and orthodontic tooth movement

The objective of orthodontic treatment is to provide a functional, stable and pleasing occlusion in harmony with overall facial esthetics (Proffit et al., 2019). Studies have shown that a great number of patients seeking orthodontic treatment are adolescent females (Xu et al., 2010). Moreover, the increased awareness of the benefits associated with a functional occlusion and a pleasant appearance has resulted in a rise in the numbers of adults seeking treatment for orthodontic problems (Melsen et al., 2012b). In the United States, one in three orthodontic patients is an adult with the majority of them being females (American Association of Orthodontists, 2019).

As orthodontic tooth movement is achieved by alterations in the balance between resorption and formation of the alveolar bone, it could potentially be modulated by any development affecting the pertinent cellular and bimolecular networks (Jiang et al., 2016; Xiao et al., 2016). The hormonal fluctuations, especially of estrogens that are observed recurrently in healthy female individuals during the menstrual cycle could further modulate periodically bone metabolism (Almeida et al., 2017). In estrogen deficient rats, orthodontic tooth movement is accelerated (Xu et al., 2010).

Thus, understanding the impact of the menstrual cycle on orthodontic tooth movement and considering the possible implications could be of benefit to the clinical orthodontist. As relevant research in human subjects presents significant practical limitations, the use of animal models could prove to be beneficial (Lelovas et al., 2008; Komori et al., 2015).

However, to the best of the authors' knowledge, evidence-based summary of the information regarding the possible effects of estrus cycle on the amount of orthodontic tooth movement in animals has not been compiled.

3. AIM

3.1. Aim of the systematic review

To systematically investigate and appraise the quality of the available evidence from animal studies regarding the effect of estrus cycle on the rate of orthodontic tooth movement.

3.2.Objectives of the systematic review

To retrieve information from animal studies regarding the effect of estrus cycle on the rate of orthodontic tooth movement.

3.3. Null hypothesis

There is no difference in the rate of tooth movement between the various stages of the estrus cycle.

4. MATERIALS AND METHODS

4.1. Protocol development

The present review was based on specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (Shamseer et al., 2015). In addition, conduct and reposting followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and green, 2011) and the PRISMA statement (Moher et al., 2009), 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 evaluating the rate of tooth movement in the different stages of the estrus cycle. Human studies, ex vivo, in vitro, in silico, non-comparative studies (case reports and case series) and reviews (traditional reviews, systematic reviews and meta-analyses) 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 female animals (with an estrus cycle) undergoing

orthodontic tooth movement. Studies on subjects undergoing any kind of orthodontic tooth movement in conjunction with other interventions such as tooth extraction, etc., on subjects after the cessation of active orthodontic tooth movement or on subjects with other co-morbidities were excluded.

4.2.3. Types of interventions

The included studies involved animals exposed to the various stages of the estrus cycle.

4.2.4. Types of outcome measures

The studies had to report the rate of orthodontic tooth movement (i.e. amount of tooth movement during a specific period of time).

4.3. Information sources and search strategy

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

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 assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. The full-text of the records considered by either reviewer to meet the inclusion criteria, were obtained and assessed, again independently, while disagreements were settled by discussion with the co-supervisor.

4.5. Data collection and data items

The main investigator and the thesis principal supervisor performed data extraction on the 7th of July 2019 independently and any disagreements were again resolved by discussion with the co-supervisor. Data collection forms were used to record the desired information.

a. Bibliographic details of the study

b. Details on the study design and verification of the 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 were needed regarding the published data, or additional material was required, then attempts to contact the corresponding authors would be made.

4.6. Risk of bias in individual studies

The main investigator and the thesis principal supervisor assessed the risk of bias in the included studies, independently and in duplicate, during the data extraction process, using the SYRCLE's risk of bias tool (Hooijmans et al., 2014). Any disagreements were resolved by discussion with the co-supervisor. The SYRCLE's risk tool assessment tool includes the following domains:

1: Was the allocation sequence adequately generated and applied?

2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?

3: Was the allocation adequately concealed?

4: Were the animals randomly housed during the experiment?

5: Were the caregivers and investigators blinded to the intervention that each animal received?

6: Were animals selected at random for outcome assessment?

7: Was the outcome assessor blinded?

8: Were incomplete outcome data adequately addressed?

9: Are reports of the study free of selective outcome reporting?

10: Was the study apparently free of other problems that could result in high risk of bias?

After entering in the data extraction form the information reported in each study, every domain received a judgment of low, high, or unclear risk of bias (Hooijmans et al., 2014).

4.7. Summary measures and synthesis of results

Though a synthesis of the results was planned according to the research protocol, it was not, in the end, carried out due to the lack of an adequate amount of data.

4.8. Additional analyses

As an insufficient number of trials was identified, analyses for "small-study effects" and publication bias (Higgins and Green, 2011) 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

The flowchart of records through the reviewing process is shown in Figure 2. The data search took place in July 2019. Initially 29 records were identified through data base screening and 24 records remained after the exclusion of the duplicates. Furthermore, 16 records were excluded on the basis of their title and abstract. The full text of 8 records was assessed for eligibility. For example (Zhao et al., 2005) was excluded for being a duplicate of an article included. Other articles (Xiaomei et al., 2010; Rui et al., 2013; Yang Xi et al., 2013; Wang Bin et al., 2014) were also excluded for being human studies. Finally, three full text reports were included in the systematic review (Haruyama et al., 2002; Guo et al., 2007; Celebi et al., 2013). The corresponding authors of the studies were contacted to provide additional information and Celebi et al. (2013) were kind enough to provide them (Appendix III).

5.2. Study characteristics

The characteristics of the included studies are presented in Table 1. They were published between the years 2002 and 2012 and investigated the influence of estrus cycle on the rate of orthodontic tooth movement. In the studies included two types of animals were used; cats (Celebi et al., 2013) and Wistar rats. An expansion spring between the upper first molars was used by Haruyama et al. (2002). The other two studies used NiTi coil springs to retract the canine (Celebi et al., 2013) and mesialize the first molar (Guo et al., 2007). The forces exerted ranged between 13-80g.

The rate of tooth movement was measured clinically (Guo et al., 2007); from silicone impressions (Celebi et al., 2013) and from tracings of the occlusal surface of maxillary

casts (Haruyama et al., 2002). No sample size calculations were performed and only Haruyama et al. (2002) assessed the error of the method.

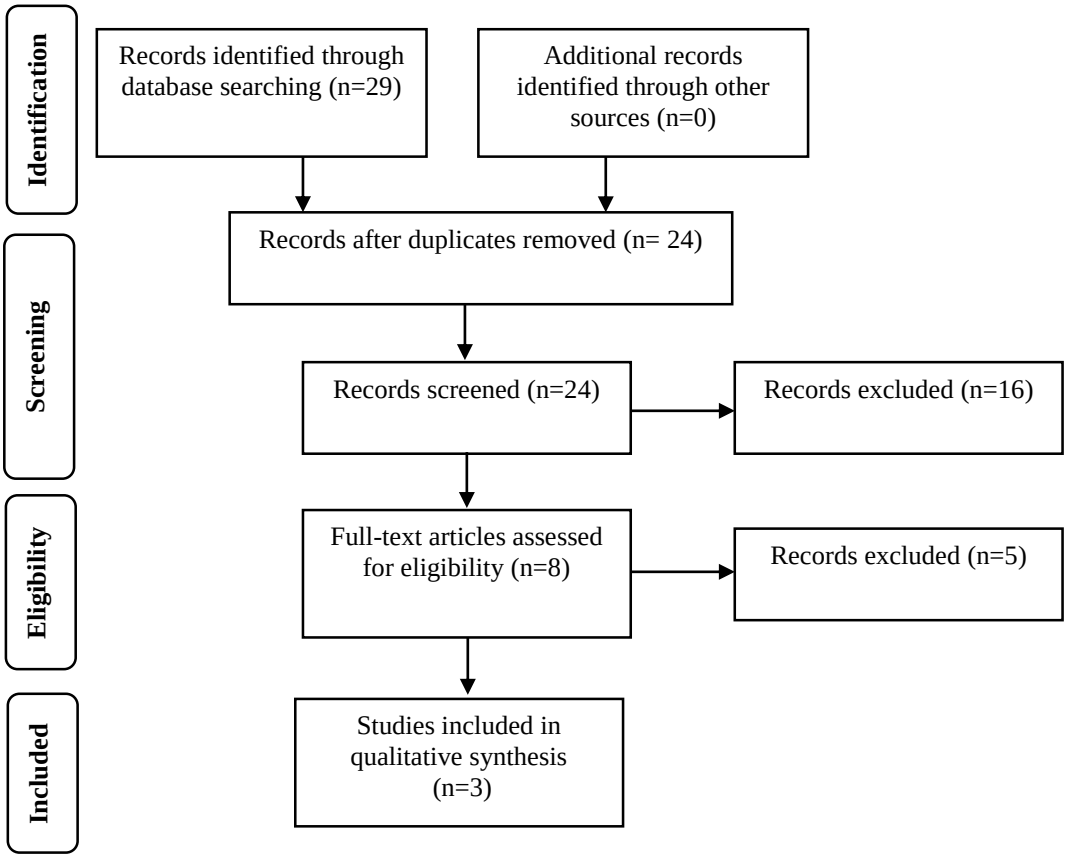

Figure 2. Flowchart of records through the reviewing process.

Table 1. Characteristics of the included studies.

Study	Subjects and tooth movement model	Group Characteristics	Measurement Methodology	Results[§§]			
Haruyama et al. 2002	Wistar rats; 10 weeks; 136g NiTi expansion spring between R and L FM [13g] **Force application**: at each stage for 5 cycles	**Proestrus Group** 8 **Estrus Group:** 8 **Metestrus Group**: 8 **Diestrus Group:** 8 **Sample size calculation:** nm	**Tracings of casts:** calipers [after each stage] **Method error assessment:** Yes	**Proestrus** **A** **Estrus > Proestrus**	**Estrus** **B**	**Metestrus** **NS**	**Diestrus** **NS**
Guo et al. 2007	Wistar rats; 3 months; 300g NiTi CCS between L Mx I and FM [50g] **Force application:** at each stage for 4 cycles	**Proestrus Group** 10 **Estrus Group:** 10 **Metestrus Group**: 10 **Diestrus Group:** 10 **Sample size calculation:** nm	**Clinically:** calipers [after each stage] **Method error assessment:** nm	**Proestrus** **A** **Estrus> Metestrus, Diestrus > Proestrus**	**Estrus** **B**	**Metestrus** **C**	**Diestrus** **C**
Celebi et al. 2013	Cats; 2-4 yrs. NiTi CCS from mini implants to Mx C [80g] **Force application:** 12d	**Estrus Group**: 6[§] **Anestrus Group**: 6 **Sample size calculation**: nm	**Silicone impressions:** digital calipers [d 0,6,12] **Method error assessment**: nm	**Estrus < Anestrus**			

d: days; CCS: closed coil spring; FM: first molars; NS: non-significant

[§] Estrus was induced by administration of 150 IU equine chorionic gonadotropin. In the anestrus group blood estradiol levels were at basal value.

[§§] The different letter denotes a statistically significant difference.

5.3. Risk of bias within studies

Table 2 represents the summary of findings regarding risk of bias assessment. The assessed domains were found to be mostly at unclear risk of bias.

The risk of bias for the domains of baseline similarity and selective outcome reporting was assessed to be low. Regarding incomplete outcome data and potential other problems, the risk of bias was assessed to be high for Haruyama et al. (2020) because of the significant number of animals excluded from the final analysis.

Table 2. Summary of risk of bias assessment.

	Signaling questions									
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Haruyama et al. 2002	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	High
Guo et al. 2007	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Celebi et al. 2013	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low

1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation adequately concealed?; 4: Were the animals randomly housed during the experiment?; 5: Were the caregivers and investigators blinded to the intervention that each animal received?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study apparently free of other problems that could result in high risk of bias?

5.4. Results of individual studies

The results of the included studies in the present systematic review showed that tooth movement was increased in the stages of the estrus cycle when the estrogen and/or progesterone levels were lower (Table 1).

Haruyama et al. (2002) and Guo et al. (2007) showed an increase in tooth movement in the estrus groups when the estradiol and progesterone levels are expected to be at their lowest.

In Haruyama et al. (2002) tooth movement was greater in the estrus group by 32.6% compared to the proestrus group ($p < 0.05$; Tukey-Kramer test). Tooth movement in the metestrus and diestrus group did not differ significantly between the two groups, as well as the other two.

Guo et al. (2007) observed 2.10 ±0.14 mm total tooth movement in the estrus stage, while the lowest result was for the proestrus stage (1.79 ±0.03 mm) ($p<0.05$). Tooth movement in the metestrus (1.94 ±0.04 mm) and diestrus (189 ±0.06 mm) groups did not differ significantly but was significantly different from the other two estrus cycle groups.

Celebi et al. (2013) showed slower tooth movement in the estrus group, but in cats this stage is characterized by increased estrogen levels (6 days, Estrus (Mean ±SD): 0.546 ±0.055 mm; Anestrus (Mean ±SD): 0.659 ±0.107 mm, $p<0.05$, ANOVA; 12 days, Estrus (Mean ±SD): 0.742 ±0.058 mm; Anestrus (Mean ±SD): 0.992 ±0.108 mm, $p<0.05$, ANOVA).

5.5. Additional analyses

It was neither possible to conduct analyses for “small-study effects” and publication bias, nor for subgroup analyses.

6. DISCUSSION

6.1. Summary of available evidence

Studies have shown that most of the patients receiving orthodontic treatment were adolescent and adult females (Jacob et al., 2004). Estrogen levels fluctuate during the menstrual cycle potentially resulting in periodical effects in alveolar bone metabolism and the rate of orthodontic tooth movement in adolescent and adult menstruating female patients (Zittermann et al., 2000). Based on the data from the animal studies retrieved in the current review, tooth movement was increased in the stages of the estrus cycle where the estrogen and/or progesterone levels were lower. Thus, the null hypothesis was not accepted. Although information from the identified few animal studies cannot be fully translated to human clinical scenarios and the risk of bias was mostly unclear, until more scientific information becomes available, clinicians should not ignore the fact that menstruating patients could exhibit differential physiological bone remodeling in different menstrual cycle stages, as well as the possible implications.

In the two rat studies, the rate of movement after the application of orthodontic forces was greater in the estrus group when estradiol and progesterone levels are expected to be at their lowest levels. Conversely it was lower in the proestrus animals when estradiol levels are supposed to peak (Haruyama et al., 2002; Guo et al., 2007). Indeed, estradiol levels varied as expected according to the estrous cycle stage, with a peak observed in proestrus and the lowest concentration during estrus (Haruyama et al., 2002; Guo et al., 2007). The rate of tooth movement was inversely related to estradiol measurements (Haruyama et al., 2002). Also, negative correlations were noted between estradiol and serum TRAP activity and pyridinoline, both markers of bone resorption (Haruyama et al., 2002). Serum progesterone exhibited a different fluctuating pattern

from estradiol, with the peak in diestrus. However, the lowest levels were measured during estrus, the same as estradiol (Haruyama et al., 2002). Serum osteocalcin, which is a marker of bone formation, showed a significant correlation with progesterone (Haruyama et al., 2002).

Celebi et al. (2013) showed slower tooth movement in the estrus group, but in cats this stage is characterized by increased estrogen levels. In this group folliculogenesis and estrus was predictably induced by the exogenous administration of equine chorionic gonadotropin (eCG) (Pelican et al., 2006). PGE2 and IL-1b concentrations were significantly increased in the anestrus animals, where the greatest tooth movement rate was observed.

Estrogens are known down-regulators of bone resorption and act to maintain bone mass (Khosla et al., 2012). In the context of orthodontic treatment, the administration of oestrogen reduced the rate of tooth movement in osteoporotic rats (Jin et al., 2000). Previous studies have confirmed that the rate of tooth movement is closely related to the activity of osteoclasts (Igarashi et al., 1994) and estrogen can inhibit it (Syed 2005). 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 (Celebi et al., 2013). Progesterone also has been reported to lead to the bone preservation results directly through action on the osteoblasts, or indirectly by influencing the glucocorticoid receptors or the metalloproteinases (Graham et al., 1997) and has been linked with reduction in the rate of tooth movement (Poosti et al ., 2009).

6.2. Strengths and limitations of the present review

The strengths of the present review include the use of a well-established methodology. The strategy employed for data retrieval from electronic and manual sources was exhaustive and comprehensive, without pre-set limitations regarding language, date and status of publication. Also, in order to eliminate possible biases, screening, verification of eligibility, abstraction of information, as well as assessment of the risk of bias were performed in duplicate, and any disagreement was resolved by discussion until a final agreement was achieved. Finally, as relevant research in human subjects presents significant practical limitations, the use of animal models could prove to be beneficial (Lelovas et al., 2008; Komori et al., 2015).

There are also some limitations to the present review, arising mainly from the nature and the characteristics of the included studies and the data retrieved during the review process. It must be kept in mind that the collected information relates to animal studies and thus cannot be directly extrapolated to humans. Significant differences between rodents and humans exist, not only in terms of bone physiology, but also of pregnancy/lactation endocrinology (Almeida et al., 2017). The lack of relevant research and power sample calculations were additional limitations affecting the precision of the retrieved results. Moreover, the use of specific modes to induce orthodontic tooth movement further circumscribes the generalizability of the retrieved information to human clinical scenarios. Also, several omissions in the report of the studies led to unclear conclusions regarding the risk of bias in various domains. Consequently, it cannot be clearly determined, whether the menstrual stage cycle can affect tooth movement in human clinical scenarios.

Even from this limited set of animal 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 must be considered that patients may present increased needs for anchorage preparation when force is applied during the phases that estrogens are at their lower levels. On the contrary, activation during these stages may promote tooth movement, thereby shortening the total duration of orthodontic treatment. Although not directly studied in the material retrieved, one could also suggest that fixed appliances should be removed during periods when high levels of estrogen or progesterone are circulating.

6.3. Recommendations for future research

Since female patients constitute the majority of orthodontic patients, additional well-designed experimental studies to investigate and understand the effect of estrus cycle on orthodontic tooth movement could be beneficial for the clinician. It is highly desirable that study designs become standardized (Kilkenny et al., 2012) and possible sources of bias receive the appropriate attention (Hooijmans et al., 2014). Besides, future investigation should simulate, as closely as it is feasible, scenarios in clinical practice in humans in terms of magnitude of force as well as the characteristics of the employed method of force delivery.

7. CONCLUSIONS

Hormonal changes during the estrus cycle may affect the rate of orthodontic tooth movement in animals. Although these animal experiment results should be approached cautiously, it could be safe practice to consider the possible impact of these physiological changes in the clinical setting until more information becomes available.

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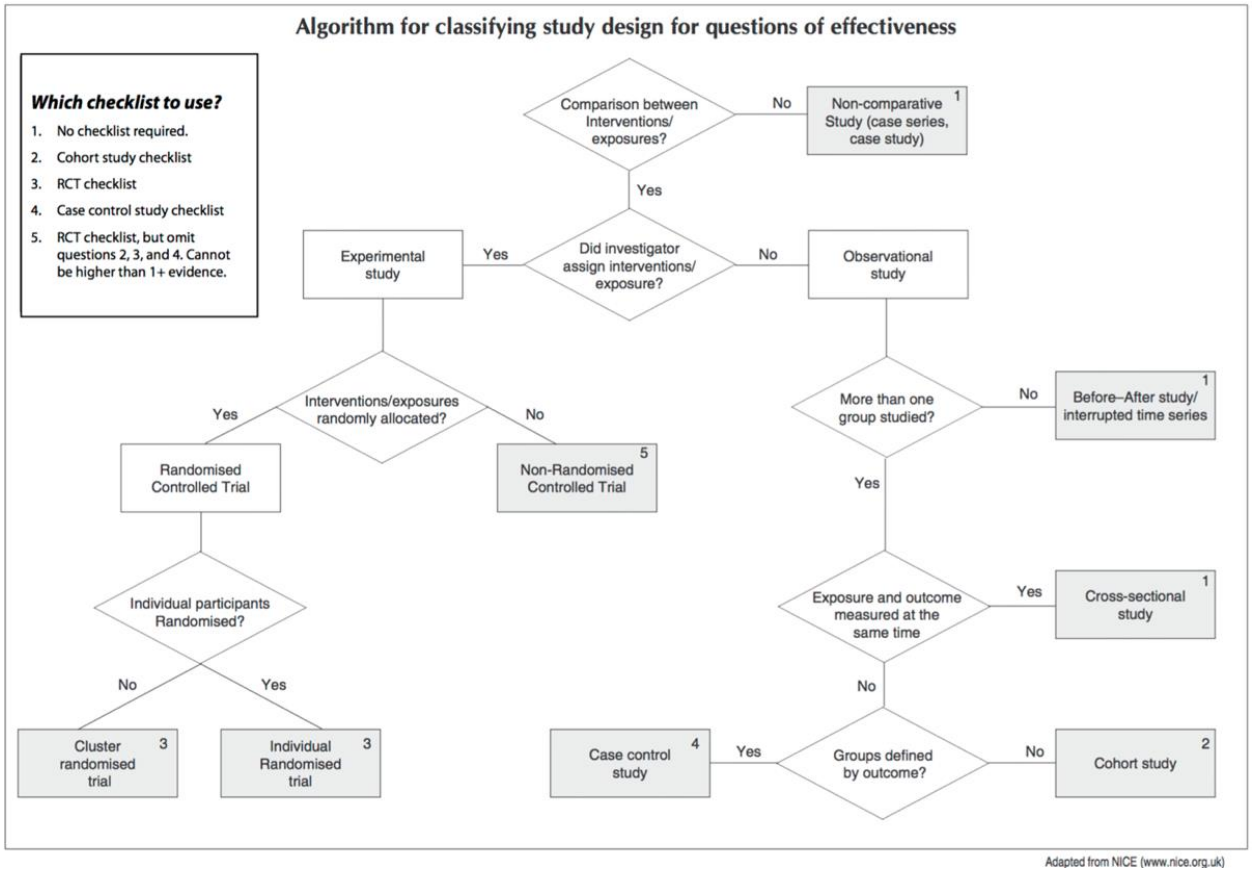
9. APPENDICES

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



Appendix II. Strategy for database search.

Database [2019 07 09]	Search strategy	Hits
PubMed http://www.ncbi.nlm.nih.gov/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 http://onlinelibrary.wiley.com/cochranelibrary/search	(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 http://0-ovidsp.tx.ovid.com.amclb.iii.com/sp-3.16.0b/ovidweb.cgi	(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 https://www.scopus.com/search/form.url?zone=TopNavBar&origin=searchbasic	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™ http://apps.webofknowledge.com/	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	**12**

	OR menstrual OR amenorrhea OR "proliferative phase" OR "secretory phase") AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)) Timespan: All years. Databases: WOS, KJD, RSCI, SCIELO, ZOOREC. Search language=Auto	
Arab World Research Source http://0-web.a.ebscohost.com.amclb.iii.com/ehost/search/advanced?sid=ff64c697-1ea0-41dc-9afe-961bc654cd05%40sessionmgr4002&vid=0&hid=4114	TI tooth movement OR AB tooth movement	**3**
ProQuest Dissertations and Theses Global http://search.proquest.com/dissertations	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**

Appendix III: Communication with authors.

Από: **Ayesha Mohammed D16** ayesha.mohammed@alumni.mbru.ac.ae
Θέμα: Fw: Enquiry on paper -
Ημερομηνία: 2 Φεβρουαρίου 2020 - 11:12
Προς: Eleftherios Kaklamanos Eleftherios.kaklamanos@mbru.ac.ae
Κοιν.: Dr. Ayesha Omar dehen_al3ood1@hotmail.com

AD

Answer of Dr. Ahmet Celebi, "Effect of ovarian activity on orthodontic tooth movement and gingival crevicular fluid levels of interleukin-1ß and prostaglandin E_2in cats"

From: aa C <ahmetarifcelebi@gmail.com>
Sent: Monday, March 11, 2019 7:43 PM
To: Ayesha Mohammed D16 <ayesha.mohammed@residents.mbru.ac.ae>
Subject: Re: Enquiry on paper

Dear Dr. Ayesha Mohammed,
I am so happy to hear that you are referring my article in your study. I have checked my files and found a excel file which can be helpful to you. However, It is prepared by Turkish language. I have attached it to below.
Have a great day.

Thanks and regards,
Dr. Ahmet A. Celebi DDS, MS, PhD

On Mon, Mar 11, 2019 at 9:39 AM Ayesha Mohammed D16 <ayesha.mohammed@residents.mbru.ac.ae> wrote:

Dear Dr. Ahmet Celebi,
I read with great interest your paper entitled "Effect of ovarian activity on orthodontic tooth movement and gingival crevicular fluid levels of interleukin-1ß and prostaglandin E_2in cats" Angle Orthod. 2013;83:70–75, this paper contains a graph that is of a great benefit to me as I'm conducting a systematic review about the effect of menopause on the rate of orthodontic tooth movement and root resorption and a possible meta-analysis.
If it is possible, can you send me the values (means ± SDs) corresponding to Figure 2.
Looking forward for your kind response.If you need any additional information, please feel free to contact me

Best Regards,
Ayesha Mohammed

Dis hareketi olcumu son.xls