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Consideration of hormonal changes for orthodontic treatment during pregnancy and lactation - a review

Yujie Zhao[1], Shengqi Qian[3], Zhijun Zheng[1], Juxiang Peng[1], Jianguo Liu[4], Xiaoyan Guan[2*] and Chengcheng Liao[2,4,5*]

Abstract
Hormonal changes in pregnant and lactating women significantly affect bone metabolism and overall stress levels, positioning them as a unique group within the orthodontic population. Fluctuations in estrogen, progesterone, prolactin, and other hormones are closely linked to bone remodeling and the periodontal tissue's response to inflammation caused by dental plaque. Hormones such as thyrotropin, leptin, and melatonin also play crucial roles in pregnancy and bone remodeling, with potential implications for orthodontic tooth movement. Additionally, adverse personal behaviors and changes in dietary habits worsen periodontal conditions and complicate periodontal maintenance during orthodontic treatment. Notably, applying orthodontic force during pregnancy and lactation may trigger stress responses in the endocrine system, altering hormone levels. However, these changes do not appear to adversely affect the mother or fetus. This review comprehensively examines the interaction between hormone levels and orthodontic tooth movement in pregnant and lactating women, offering insights to guide clinical practice.

Keywords Hormone, Pregnancy, Lactation, Orthodontic, Bone remodeling

*Correspondence:
Xiaoyan Guan
1278279125@qq.com
Chengcheng Liao
lcc_950330@163.com
[1]Department of Orthodontics, Guiyang Stomatological Hospital, No.253 Jiefang Road, Nanming District, Guiyang, Guizhou Province 550002, China
[2]Department of Orthodontics II, Affiliated Stomatological Hospital of Zunyi Medical University, No.143 Dalian Road, Huichuan District, Zunyi, Guizhou Province 563000, China
[3]Department of Stomatology, Guizhou Provincial People's Hospital, No.23 Zhongshan East Road, Nanming District, Guiyang, Guizhou Province 550002, China
[4]Oral Disease Research Key Laboratory of Guizhou Tertiary Institution, School of Stomatology, Zunyi Medical University, Zunyi 563006, China
[5]West China School of Stomatology, Sichuan University, Chengdu 610000, China

Introduction
With the increasing public demand for facial beauty, the number of adult female patients seeking orthodontic treatment exceeds that of male patients due to concerns such as protruding teeth, gaps between teeth, crowded teeth, and an unsightly smile [1]. The lengthy duration of orthodontic treatment poses challenges for women of childbearing age, particularly if they become pregnant during the treatment period. Pregnancy and lactation in female orthodontic patients introduce risks that may affect the progress of treatment and potentially impact both the mother and fetus.

A significant feature of pregnancy and lactation is the dramatic change in hormone levels. Current studies confirm that these hormonal changes significantly influence bone metabolism and inflammation in the body. The rate of orthodontic tooth movement (OTM) can be regulated

by pathways related to bone metabolism. Therefore, adaptive changes in bone homeostasis during pregnancy and lactation, along with the balance between osteoclast activity and osteoblast deposition, may affect OTM. Hormone levels also regulate susceptibility to oral diseases. Since the 1960s, researchers have linked pregnancy to periodontal health, with gestational gingivitis being the most common oral manifestation of pregnancy, affecting 35–100% of pregnant women [2]. Poor oral hygiene and hormonal influences during pregnancy may increase the risk of recurrent oral granuloma gravidarum (OGG) and gingivitis [3, 4]. Additionally, pregnancy significantly affects tooth mobility, with the highest mobility occurring in the third trimester [5]. During lactation, the influence of estrogen and prolactin (PRL) enhances female bone turnover, resulting in a negative balance of bone homeostasis [6]. Excessive orthodontic force may further reduce alveolar bone density [7]. Thus, hormone levels may regulate the speed of tooth movement during pregnancy and breastfeeding. Moreover, orthodontic treatment may pose potential safety concerns for the mother or fetus during these periods.

Currently, an increasing number of clinical studies are focusing on the impact of menstrual sex hormone changes on tooth mobility [8, 9] and OTM [10, 11]. The hormonal fluctuations during pregnancy and lactation are more significant and prolonged. Understanding the influence of these hormonal changes on OTM will provide valuable guidance for clinical practice. Therefore, this article explores the interaction mechanism between hormone levels and OTM, which is crucial for clinical diagnosis and treatment. This research aims to raise awareness among orthodontists about the specific considerations for treating pregnant and lactating women, ultimately reducing risks for both patients and practitioners.

Effects of hormone changes during pregnancy and lactation on OTM

Effect of estrogen and progesterone on OTM during pregnancy

Effect of estrogen on PDLSC and PLFs

Pregnancy is a unique state of continuous adaptation of maternal physiology, involving changes in metabolism, hormone levels, inflammatory status, nutritional needs, and the immune system [12]. Estrogen and progesterone levels fluctuate significantly during pregnancy. Estrogen, a steroid hormone secreted by the ovary and placenta, includes estrone, estradiol, and estriol. Among these, estradiol has the strongest biological activity and the most clinical applications. Serum concentrations of estradiol range from 188 to 2497 pg/mL during the first trimester, reaching up to 7192 pg/mL by term [13]. Compared to non-pregnancy levels, estrogen increases

tenfold, while progesterone increases thirtyfold [14]. Estrogen plays a unique role in oral diseases, with its expression varying across different life stages in women. For instance, high estrogen levels during pregnancy can alter oral microbiota, promoting gingivitis, while low estrogen levels after menopause can exacerbate temporomandibular joint degradation and increase alveolar bone loss [15]. Recent studies have shown that pregnancy-related hormones can affect periodontal tissue remodeling by acting on related stem cells and immune cells in periodontal tissue (Table 1).

Periodontal stem cells (PDLSCs), isolated from the periodontal ligament—a connective tissue that links cementum and alveolar bone and restricts tooth movement within the jaw bone—can differentiate into various cell types. PDLSCs play a crucial role in periodontal reconstruction, including bone formation. Estrogen receptor (ER) α and β are involved in the osteogenic differentiation of PDLSCs and are vital for bone formation [16]. Estrogen binds to ERs on the PDLSC cell membrane to regulate intracellular signal expression, promoting PDLSCs proliferation and osteogenic differentiation, thereby facilitating the repair and re-adhesion of periodontal ligament fibers to new cementum and reconstructed alveolar bone [17] In addition, estrogens bind to ERα and ERβ of the cell membranes of PDLSCs, promoting cell proliferation and differentiation into periodontal ligament fibroblasts(PLFs), osteoblasts, and cementoblasts [18, 19]. Studies indicate that changes in bone metabolism during pregnancy and lactation, and osteoporotic changes due to estrogen deficiency, may affect the rate of tooth movement [20, 21].

The potential impact of estrogen deficiency on the osteoblastic differentiation of PDLSCs was investigated using bilateral ovariectomy (OVX) in female rats. It was found that the activity of alkaline phosphatase (ALP), secretion of osteocalcin (OCN), mineral formation, and mRNA expression levels of ERα and ERβ were significantly decreased in the OVX group. The addition of estradiol significantly suppressed the proliferation of PDLSCs in ovariectomized rats but enhanced their osteogenic differentiation and increased mRNA expression levels of ALP, OCN, ERα, and ERβ [22]. These results indicated that estrogen enhanced the bone regeneration potential of PDLSCs in rats and was beneficial to the osteogenic differentiation of PDLSCs.

Estrogen not only acts on PDLSCs but also regulates the formation of osteoblasts and osteoclasts. Estradiol may inhibit tooth movement through an ERα-mediated mechanism, as evidenced by increased osteoclast numbers and decreased osteoblast numbers during tooth movement in ERα-deficient mice [23]. Compared to gingival fibroblasts (GFs), the addition of estradiol significantly inhibited the formation of osteoclast-like cells

Table 1 Effects of hormonal changes during pregnancy on related cells during OTM

Hormones/cells	PDLSCs/Osteoblasts /hPDLCs	PLFs/ Osteoclasts	Macrophage	Cementoblast /GFs
estrogen	Promote PDLSCs proliferation and differentiation into PLFs, osteoblasts and cementoblasts.	Inhibit the formation of osteoclast-like cells induced by PLFs	Promote the differentiation of macrophages into M2 type and up-regulate the expression of anti-inflammatory markers; Inhibition of M1-type macrophages expression of inflammatory factors to reduce the degree of inflammation	Promote the proliferation of cementoblast, promote the formation of new cementum, inhibit root resorption and promote root regeneration
		Inhibit the activity of osteoclasts		
progesterone	Promote proliferation and osteogenic differentiation of hPDLCs; Acts directly or indirectly on osteoblasts to downregulate bone resorption			It may inhibit the periodontal tissue repair process mediated by GFs
prolactin	Induction of osteoblasts increased the expression ratio of RANKL/OPG and induced bone loss in adults	It indirectly promotes the differentiation of osteoclasts		
thyroid stimulating hormone	Activate osteoblasts	Inhibition of osteoclast differentiation down-regulates the expression level of TRAP		
leptin	Promote osteoblast differentiation;The RANKL expression and RANKL/OPG ratio in PDLCs were inhibited, thereby inhibiting the generation of osteoclasts	PDLF could indirectly affect the formation of osteoclasts.	Promote the differentiation of macrophages into M2 type, up-regulate the expression of anti-inflammatory markers, and reduce the degree of inflammation	It affects the normal mineralization of cementoblast and aggravates the physiological effect of pressure on cementoblast
melatonin	Promote osteogenic differentiation of hPDLCs; Enhance osteoblast differentiation	The OPG/RANKL ratio was increased to inhibit osteoclast differentiation. Enhance the expression of PDLF inflammatory cytokines	Promote the differentiation of macrophages into M2 type, up-regulate the expression of anti-inflammatory markers, and reduce the degree of inflammation	

induced by PLFs. The number of tartrate-resistant acid phosphatase (TRAP)-labeled osteoclast-like cells was significantly reduced [24]. Estrogen and ER specifically bind to form a hormone-receptor complex that promotes the proliferation and differentiation of osteoblasts, inhibits the activity and generation of osteoclasts, and participates in bone metabolism through ER-related signal transduction pathways. The effect of estrogen on osteoblasts and osteoclasts lays the foundation for its regulation of OTM.

Effect of estrogen on macrophages

The speed of tooth movement is closely related to the activity of osteoclasts. Macrophages, as part of the monocyte-macrophage system, regulate osteoclasts under certain conditions [25]. Based on their activation state and function, macrophages are mainly classified into classically activated M1 type and selectively activated M2 type [26]. The phenotypic phases of macrophages play different roles in the OTM process. Initially, macrophages are recruited to the inflammatory site, where various inflammatory factors promote their polarization towards the M1 type, aggregating on the compressed side of the periodontal tissue [27, 28]. M1 macrophages accelerate OTM by overexpressing TNF-α and inducing inducible nitric oxide synthase (iNOS) to promote inflammation [27]. During the early stage of tooth movement, the expression of M1 macrophages increases and remains elevated for a period [27], while M2 macrophages, which promote tissue repair, do not significantly increase until the later stage [28]. In the early stage of OTM, M1 macrophages predominate, while in the late stage, M2 macrophages accumulate significantly, which is critical for the cessation of bone resorption and the initiation of tissue repair. Estradiol significantly decreases the gene expression of inflammatory markers and the production of IL-1β in M1 macrophages, while significantly upregulating anti-inflammatory markers and enhancing migration in M2 macrophages [29]. The promotion of M2 macrophages by estradiol may aid periodontal tissue repair during OTM. Estrogen not only affects alveolar bone remodeling by acting on PDLSCs and PLFs but also regulates bone metabolism by influencing macrophage expression of inflammatory factors. Additionally, estrogen inhibits root resorption and promotes root regeneration, protecting root integrity during orthodontic treatment [30]. However, there is a lack of research on the differences in root

resorption between pregnancy and non-pregnancy under high estrogen levels.

Potential effects of estrogen on temporomandibular joint

Estrogen is a hormone that plays a key role in various physiological processes, including bone and joint health. ER are present in the temporomandibular joint (TMJ) and are unevenly distributed, performing different functions [31]. Estrogen levels affect the structure and function of the TMJ. Estrogen signaling is complex, involving different pathways that may promote anabolism of mandibular condylar fibrocartilage or mediate facial pain [15]. The health and function of articular condylar fibrocartilage are crucial for bearing and redistributing the load on the subchondral bone. Damage to this fibrocartilage leads to TMJ degeneration. Estrogen reduces the thickness of joint fibrocartilage by inhibiting chondrocyte proliferation and promoting chondrocyte maturation [32], while progesterone may be essential for joint remodeling, for morphogenesis [33]. Thus, estrogen plays a critical role in maintaining the integrity of temporomandibular joint cartilage.

Estrogen levels fluctuate significantly during pregnancy, and many studies have investigated the association between pregnancy and the prevalence of temporomandibular joint disorder (TMD) [34]. TMD encompasses a variety of conditions affecting the TMJ and its associated muscles. These disorders affect approximately 15% of adults, are most common between the ages of 20 and 40, and often present with symptoms such as jaw discomfort, dysfunction, earache, facial pain, and headache [34, 35]. The etiology of TMD is multifactorial, influenced by biological, environmental, social, and psychological factors [36]. Estrogen may have a biphasic effect on TMD, with high and/or fluctuating levels promoting some types of TMD and low levels exacerbating others [15].

Pregnancy induces a range of physiological changes in women, including hormonal fluctuations, weight gain, and postural adjustments, all of which can affect TMD [15]. Hormonal changes during pregnancy may impact the TMJ and its surrounding structures. Studies have shown that TMJ relaxation increases and musculoskeletal maxillofacial pain decreases during pregnancy [37]. Estrogen plays a role in TMD-related pain, with chronic pain levels being highest when estrogen levels are lowest. As pregnancy progresses, pain decreases, reaching its lowest at 36 weeks of gestation [38]. Estrogen deficiency is associated with increased pain sensitivity, and experimental studies indicate that high levels of estrogen and progesterone have anti-nociceptive properties [39]. Fluctuating estrogen levels can make women more prone to prolonged pain [15].

Earlier studies indicated that TMD primarily affects women of reproductive age, suggesting that higher estrogen levels might aggravate the condition [37, 40]. However, two longitudinal studies have shown that oral and facial pain significantly decreases during the third trimester [35] and increases postpartum [41]. Recent studies have also found that TMD pain decreases when estrogen levels are elevated, and the prevalence of TMD in pregnant women is 2–3 times lower than in non-pregnant women [42]. This suggests that TMD-related pain decreases with elevated estrogen levels. One possible explanation for the inconsistent outcomes of pregnancy and hormone replacement therapy is altered tissue sensitivity to estrogen level fluctuations rather than the concentration levels themselves [43].

Some studies have suggested that elevated estrogen levels may increase the risk of TMD, while others have found no such association. Evidence indicates that TMD mainly affects women of reproductive age, implying that higher estrogen levels increase TMD risk [37]. However, a recent systematic review found no significant difference in TMD prevalence between pregnant and non-pregnant women of reproductive age [44]. A case-control cross-sectional study also indicated that pregnancy is neither a risk factor nor a protective factor for TMD [45]. Differences in diagnostic criteria may have contributed to the variations in prevalence reported across studies.

In general, estrogen is involved in the anabolism of condylar fibrocartilage and mediates TMD-related facial pain. Estrogen levels fluctuate significantly during pregnancy, and orthodontists must recognize that these hormonal changes can impact orthodontic treatment through their potential effects on the TMJ. Additionally, painful TMD is associated with higher levels of emotional distress, making it essential to routinely assess physical, psychological, and social distress, particularly stress and quality of life, in patients with painful TMD [46]. Pregnant women often face various stressors that can affect both maternal and fetal health. Differences in pain perception, functional status, and mental health have been observed in pregnant women [45]. Studies have found a significant correlation between depression and several TMD-related indicators, indicating that higher depression scores correlate with greater TMD severity [45]. Therefore, the mental health of pregnant women should be closely monitored during orthodontic treatment, as depression-related joint symptoms may affect the treatment process.

Effect of progesterone on periodontal tissue

Progesterone, produced by the follicle, primarily ensures the implantation of the fertilized egg and maintains pregnancy. During pregnancy, levels of sex hormones such as progesterone and estrogen rise sharply, altering metabolism and immune function, which may affect the growth of oral microorganisms [47]. This makes

women more susceptible to periodontal diseases during pregnancy [12, 48]. Pregnancy-related gingivitis is associated with increased concentrations of progesterone, which enhances the growth of *Prevotella intermedia*, the most common bacteria in pregnancy-induced gingivitis [49]. Elevated levels of estradiol and progesterone in saliva are associated with a 55-fold increase in the proportion of *Prevotella intermedia* throughout pregnancy [50]. Additionally, estradiol and progesterone may affect gingival homeostasis and wound healing [51]. High levels of progesterone during pregnancy downregulate IL-6 production, reducing the gingiva's efficiency in resisting inflammatory challenges produced by bacteria to 40–50% of control IL-6 production in the third trimester [52]. GFs are active participants in the oral immune response, producing multiple chemokines and large amounts of matrix metalloproteinases after exposure to IL-1β. GFs attract neutrophils, monocytes, eosinophils, and fibroblasts to injured areas and contribute to wound repair. Female sex hormone concentrations, especially progesterone, significantly affect these signaling systems [53]. Elevated progesterone significantly inhibits matrix metalloproteinase production in GFs in response to IL-1β, reducing periodontal tissue destruction, which may explain why pregnancy-related gingivitis rarely progresses to periodontitis [54]. Hormone levels influence the oral inflammatory state, increasing the burden on periodontal tissue during orthodontic treatment. Veynachter et al. [55]. reported a case of recurrent oral pregnancy granuloma during two pregnancies and four times during orthodontic treatment. Despite multiple surgical resections during pregnancy, the patient successfully delivered and completed orthodontic treatment. Progesterone not only affects gum inflammation but also regulates osteoblasts. It can stimulate the proliferation and osteogenic differentiation of human periodontal ligament cells (hPDLCs), suggesting its important role in maintaining alveolar bone mass [56]. He et al. [57]. showed that increased progesterone during pregnancy enhances vascular reactivity and osteogenesis, beneficial to OTM, leading to extended follow-up times and reduced orthodontic force in clinical practice without significantly prolonging the treatment duration. Currently, large-sample clinical studies on orthodontic treatment of pregnant women are lacking, necessitating further research on the entire course of treatment and potential complications.

Effect of estrogen and progesterone on OTM velocity
Hormone levels are closely related to bone metabolism, and the bone remodeling processes during pregnancy involve multiple hormonal and biological factors [58, 59], which may affect the rate of OTM under orthodontic forces. Most existing studies on OTM during pregnancy focus on the correlation between hormones and

OTM and the expression changes of inflammatory factors during this process. Both estradiol and progesterone can affect bone turnover [60]. A systematic review of basic studies found that OTM rates increase when estrogen and progesterone levels are low during the menstrual cycle [61]. Estrogen can inhibit bone remodeling by reducing the formation of osteoblast and osteoclast precursors from bone marrow, thereby decreasing the rate of alveolar remodeling [62]. It has been reported that estrogen deficiency can accelerate OTM [63], whereas estrogen supplementation may slow it down [64, 65]. Long-term hormone drug consumption can reduce tooth mobility and increase tooth stability in the alveolar bone [9]. Animal studies have shown that the rate of OTM during pregnancy is controversial, with most opinions suggesting that bone remodeling is active and OTM rates increase after the application of corrective force during pregnancy [66–69]. However, Ghajar et al. [70]. found no statistically significant difference in the amount of OTM between pregnant and non-pregnant groups after the application of orthodontic force. Moaza et al. [20]. also reported an overall increase in OTM in the pregnant group, but it did not reach statistical significance. The number of osteoclasts is also controversial at the histological level. Ghajar et al. [70]. reported a significant reduction in the number of osteoclasts in pregnant rats, while Hessling et al. [67]. did not show a significant difference in the number of osteoclasts during pregnancy. The controversial results of these studies may be related to the complex physiological changes during pregnancy, which are influenced by multiple factors and differences in experimental design, making it difficult to compare the results or reach consistent conclusions.

In addition to the effects of estrogen changes, the expression of osteopontin increases in pregnant rats during orthodontic treatment. The intensity of osteopontin expression varies significantly at different stages of pregnancy, with the highest expression in the second trimester and the lowest in the first trimester. Osteopontin can affect OTM by promoting alveolar bone resorption on the pressure side [69]. Additionally, progesterone can act directly on osteoblasts to downregulate bone resorption and indirectly through glucocorticoid receptors and metalloproteinases [71]. Some studies have found that long-term injection of progesterone can reduce the speed of tooth movement in rabbits [72], and He et al. [68]. have shown that increasing progesterone during pregnancy is beneficial to OTM. Progesterone affects bone resorption and deposition through direct and indirect effects, and its impact on OTM may depend on whether the balance of bone homeostasis is positive or negative. Although estrogen and progesterone have protective effects on bone mass during pregnancy, maternal bone mineral density tends to decline due to increased demand

[15, 59]. From this perspective, the acceleration of OTM during pregnancy is reasonable, but this still needs verification with large sample studies. Besides the regulation by estrogen and progesterone, many other hormonal and biological factors are involved in bone remodeling during pregnancy, which may alter the rate of OTM [58]. Due to the expression of estrogen receptors in periodontal tissue, hormonal changes during pregnancy may lead to water retention [73]. Therefore, when mechanical forces are applied, the periodontal membrane of pregnant individuals may become easily compressed, facilitating the inclined movement of the teeth [67]. These studies suggest that in addition to the overall regulation of bone remodeling during pregnancy, local changes in periodontal tissue may also explain the observed changes in OTM during pregnancy.

Effects of prolactin on OTM during lactation

Lactation is characterized by increased PRL levels and estrogen deficiency, with the delivery of the placenta leading to decreased levels of estradiol and progesterone [74]. High levels of PRL inhibit the hypothalamic-pituitary-ovarian axis, reducing estrogen release and contributing to weakened bone function and increased bone resorption during lactation [75]. Estradiol deficiency is associated with greater root resorption during OTM [29]. Studies using ovariectomized models to simulate estrogen deficiency have found that this condition accelerates tooth movement [18]. the number of TRAP-labeled osteoclasts increased, and OTM accelerated, likely due to the acceleration of alveolar bone remodeling [76, 77]. However, the administration of estrogen can reduce the speed of tooth movement in osteoporotic rats [29]. Estrogen's role in mediating periodontal disease is bidirectional: high estrogen levels promote gingivitis and protect bone mass, while low levels enhance alveolar bone loss. During lactation, due to the lack of estrogen, bone mineral density is lower than during pregnancy and non-pregnancy, and the rate of OTM under a light force of 50 g is significantly accelerated [78]. Macari et al. [79]. reported that lactation promotes the differentiation of osteoclasts and osteoblasts from bone marrow cells, accelerating the physiological remodeling and OTM of the maxillary bone. This accelerated bone remodeling is related to the increased expression of the receptor activator of NF-κB (RANK)/receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) signaling pathway in alveolar bone. RANKL is a key cytokine responsible for osteoclast differentiation, activity, and survival. RANKL binds to RANK on osteoclast precursors to promote bone resorption, while OPG can bind to RANKL and prevent its interaction [80]. These findings align with previous studies showing increased expression of these factors in the crania of lactating mice and in osteoblast-like cells treated with PRL. In addition to estrogen deficiency, the direct effect of PRL on bone metabolism has also been associated with bone loss in women during lactation [81, 82].

During lactation, increased PRL levels exhibit a pro-absorptive effect, leading to bone mass reduction. While stimulating the proliferation and differentiation of breast cells, PRL also regulates bone resorption by influencing sex hormone levels [83]. The increase in osteoclast numbers and accelerated bone remodeling during lactation may be partly attributed to PRL promoting osteoclast differentiatio [84]. However, studies indicate that osteoclasts do not express the prolactin receptor (PRLR), whereas osteoblasts do express PRLR [85]. Thus, PRL's effects on osteoclasts are indirect, with PRL's influence on osteoblasts being essential for normal bone formation and bone mass maintenance [85]. Furthermore, PRL can induce osteoblasts to increase the expression of RANKL, monocyte chemoattractant protein-1 (MCP-1), cyclooxygenase-2 (COX-2), TNF-α, and IL-1 [86], potentially contributing to bone loss during lactation. PRL-PRLR interactions directly increase bone turnover by elevating the RANKL/OPG ratio [87]. The effects of PRL on osteoblasts differ between adult and juvenile animals. In adult osteoblasts, PRL increases the RANKL/OPG expression ratio, inducing bone loss, while in fetal bone cells, PRL promotes bone formation and decreases the RANKL/OPG ratio in both rat and human cells [88]. Influenced by estrogen and PRL, lactation is characterized by enhanced bone turnover, with a more significant increase in bone resorption indexes than in bone formation indexes, resulting in negative bone homeostasis [6], and accelerated OTM [20]. Hormonal changes during lactation enhance bone turnover, potentially increasing tooth mobility, but also posing challenges with higher anchorage requirements. Therefore, it is essential to closely monitor anchorage control in orthodontic patients during lactation.

There are two main stages of skeletal changes related to reproduction: an increase in bone mass during early pregnancy and a loss of bone mass in late pregnancy and lactation, ultimately providing calcium for milk production [89]. During lactation, mothers supply an average of 200–250 mg/day of calcium to their infants to support bone development, with mothers of twins or triplets losing two to three times more calcium daily [90]. Insufficient dietary calcium intake necessitates increased mobilization of maternal bone metabolism to maintain calcium balance in breast milk, potentially leading to decreased bone mineral density (BMD) [91]. A reduction in BMD can accelerate OTM while reducing orthodontic force-induced root strain and the formation of resorption pits in the cementum, thus lowering the risk of root resorption during OTM [77, 92]. Hormonal

changes and increased calcium demand during lactation may work together to accelerate OTM by decreasing BMD. However, the relationship between calcium intake during lactation and BMD remains controversial. Studies have shown that breastfeeding does not affect alveolar bone density when dietary calcium levels are normal [93]. Zhang et al. [94]. divided 150 lactating women into low, medium, and high calcium groups and found no significant differences in BMD and bone mineral content (BMC) after 12 months, indicating that calcium intake during lactation does not affect bone resorption. Other studies have found that different levels of calcium supplementation during lactation do not affect calcium content in breast milk [90, 95]. Excessive calcium intake during pregnancy and lactation may impact offspring development, with long-term calcium supplementation in rural Gambian women resulting in sex-specific bone effects in preadolescent offspring [96]. The optimal calcium-to-phosphorus molar ratio for proper bone development is considered to be 1:1 [97]. In many countries, phosphorus intake exceeds the recommended dietary intake, while calcium intake often falls below recommended levels [97]. Animal studies have shown that increased dietary calcium and phosphorus levels in pregnant and lactating mice have resulted in sex-specific differences in craniofacial size, shape, and temporomandibular joint development in offspring [98]. While studies on bone metabolism related to lactation yield varying conclusions, they suggest that abnormal bone metabolism may persist throughout lactation [99]. Numerous factors affect BMD changes during lactation, and it remains controversial whether increased dietary calcium intake improves BMD in pregnant and lactating patients. Further study is needed to determine the effects of calcium supplementation (increasing Ca: P ratio) on craniofacial morphology, development of malformations, and OTM in pregnant and lactating patients.

Potential hormones that influence OTM during pregnancy

Thyroid stimulating hormone

Hormones related to pregnancy fluctuate as the pregnancy progresses. Human chorionic gonadotropin (HCG), secreted by the placenta, increases gradually in early pregnancy and typically peaks at 8 to 10 weeks. Variations in HCG levels affect the secretion of thyroid-stimulating hormone (TSH) and other steroid hormones, with TSH concentrations being inversely correlated with HCG levels [100]. TSH levels decrease to their lowest in early pregnancy and gradually rise during mid to late pregnancy. TSH influences bone metabolism both indirectly, by regulating thyroid hormone levels, and directly, by activating osteoblasts and inhibiting the formation and function of osteoclasts. It can prevent bone

loss and restore bone density lost after OVX. Studies on ovariectomized rats have shown improvements in bone microstructure and prevention of osteoporosis following intermittent low-dose TSH injections [101]. Alkaline phosphatase and TRAP activity levels are key indicators of bone metabolism. Research has shown high activity levels of alkaline phosphatase and TRAP in the periodontal tissue of rats during early pregnancy, although the specific mechanism remains unclear [66]. TSH plays a significant role in bone remodeling during pregnancy. In vitro studies have found that TSH can inhibit osteoclast differentiation and down-regulate TRAP expression [102]. This suggests that the gradual decrease in TSH levels during early pregnancy may shift the bone metabolism balance toward bone resorption. Therefore, it can be inferred that the hormonal changes during early pregnancy may promote tooth movement. However, there is limited literature on the relationship between TSH and OTM during pregnancy.

Leptin

OTM is a sterile inflammatory process characterized by osteogenesis on the tension side and resorption on the pressure side. When orthodontic force is applied to the tooth and transmitted to the periodontal tissue, it triggers a series of biological signals that remodel the alveolar bone, allowing the tooth to move to a new position during periodontal repair. Cytokines are key biochemical mediators in this process, playing a crucial role in tooth movement. Leptin, a 16 kDa non-glycated polypeptide hormone, is primarily produced by adipocytes, with smaller amounts produced by the placenta, stomach, osteoblasts, and salivary glands [103–105]. Leptin serves dual roles as a hormone and a cytokine, and is essential in the hypothalamus's regulation of food intake, fat storage, and weight maintenance. As a cytokine, leptin is critical in bone remodeling, resorption, and new bone formation [105]. It directly influences bone metabolism by inducing the differentiation of bone marrow mesenchymal stem cells into osteoblasts [106, 107], down-regulating RANK produced by monocytes to inhibit osteoclast formation [108], and stimulating the central nervous and neuroendocrine systems to release corresponding mediators [109]. Leptin is involved in anti-osteogenesis through its central action on the hypothalamus [110]. In vitro studies have shown that continuous leptin stimulation in mice interferes with normal cementoblast mineralization, exacerbates the physiological stress effects on cementoblasts, promotes the release of prostaglandin E2, and increases apoptosis rates [111]. Therefore, elevated leptin levels may affect the inflammatory response during OTM.

Leptin can indirectly affect osteoclast formation by acting on PDLF, thereby influencing OTM. Leptin

significantly increases the expression of RANKL in PDLF under mechanical force, with stress-induced pro-inflammatory factors rising as leptin concentration increases, thus accelerating OTM [112]. However, Yan Boxi et al. [113]. reported that peroxisome proliferator-activated receptor γ (PPAR-γ) and Wnt signaling might be involved in leptin's regulation of OTM. Leptin can inhibit the expression of RANKL and the RANKL/OPG ratio in PDLCs through its receptor, thereby inhibiting osteoclast formation and slowing OTM. Additionally, leptin coordinates the host response to inflammatory and infectious stimuli and stimulates the immune system by enhancing cytokine production and macrophage phagocytosis [114]. Macrophages, which are inflammatory-mediated immune cells that promote osteoclast formation by interacting with PDLF, play a significant role in tooth movement. Leptin affects the expression profile of macrophages depending on mechanical load. Without mechanical stress, macrophages exhibit a pro-inflammatory phenotype (M1), but under mechanical stress, they transform into an anti-inflammatory phenotype (M2). The inhibition of inflammatory factor expression may reduce aseptic inflammation and thus slow OTM [115]. Leptin is found in both inflamed and healthy gum tissue. Clinical trials and basic studies have reported changes in leptin concentration in gingival crevicular fluid (GCF) during OTM. Leptin concentration initially increases and then decreases during the early stages of tooth movement, falling below baseline after one month [116]. Most studies show a positive correlation between GCF leptin concentration and OTM velocity [116–119]. However, some reports indicate that OTM reduces leptin concentration in GCF, with leptin levels decreasing as teeth move, contradicting earlier findings [118, 120, 121]. These studies differ in experimental design (age of subjects, force size, sampling time, etc.), and patients may have varying leptin levels throughout the day due to leptin's circadian rhythm [105]. Additionally, leptin levels differ among patients with different types of malocclusion. Compared to Class I patients, those with Class II and III malocclusions have higher salivary leptin levels [122]. Therefore, while the conclusions of these studies are difficult to compare, they all suggest that leptin is involved in regulating OTM.

Pregnancy is a metabolically demanding state for the body, requiring it to meet the energy needs of both the growing fetus and itself. Leptin, a key regulator of appetite and metabolism, links the body's nutritional status to the process of high energy consumption and regulates satiety and energy homeostasis [123], which is particularly important during pregnancy and regulating the body's satiety and energy homeostasis. During pregnancy, leptin produced by the placenta significantly contributes to the high concentration of circulating leptin levels in the mother [124]. Leptin concentrations peak in the second trimester and decline sharply postpartum [125]. Leptin, primarily released by adipose tissue, is a product of obesity genes, and there is a strong positive correlation between serum leptin concentration and body mass index (BMI) or fat mass [126]. Pregnancy increases food intake and fat deposition in mothers, often leading to an increase in BMI. In overweight or obese individuals, increased fat elevates serum leptin levels, which can further affect bone remodeling [127, 128]. The expression of leptin varies with different body weight states, and an increased BMI may impact OTM [129]. Existing studies show controversies regarding leptin levels and OTM speed in patients with increased BMI. Elevated leptin concentrations in obese patients, along with increased pro-inflammatory factors, RANKL, and osteoclast production, can accelerate bone resorption and thus OTM [112].

In a clinical experiment, Jayachandran et al. [119] observed that the average leptin concentration of 30 female subjects, both normal weight and overweight, significantly increased compared to baseline values at the initial stage. Overweight subjects had higher average salivary leptin concentrations than normal weight subjects, but their OTM velocity was lower. The slower OTM in obese patients with increased leptin concentrations may be attributed to leptin's direct stimulation of bone formation, which may have a more significant impact on bone mass and delay OTM compared to its peripheral role through hypothalamic inhibition.

The prevalence of gingivitis and increased BMI during pregnancy can affect leptin concentration [130], which in turn influences bone metabolism and OTM. However, there is limited evidence on how fluctuations in leptin levels during pregnancy affect OTM and whether orthodontic interventions impact leptin levels.

Melatonin

Melatonin, also known as the "dark hormone," is a neuroendocrine hormone synthesized in various organs, including the pineal gland and salivary glands, but primarily secreted by the pineal gland in the dark [131]. Melatonin levels are lower during the day due to its rapid breakdown and reduced production in daylight [132]. It plays crucial roles in regulating energy expenditure, body weight, normal pregnancy, and fetal development [132, 133]. During pregnancy, melatonin is endogenously produced in the ovaries and placenta, with the placenta being the main source [134]. Systemic melatonin levels are higher in pregnant women than in non-pregnant women, gradually increasing during gestation and peaking at term, then dropping to non-pregnant levels two days postpartum [134, 135]. Women with twin pregnancies have significantly higher melatonin levels compared

to those with single pregnancies [136]. Melatonin is essential for adequate placental perfusion, preventing vascular damage, reducing oxidative stress and inflammation, and maintaining a favorable homeostasis environment in the placenta [135, 137]. It also influences the timing of natural labor and uterine contractions. In the first and second trimesters, melatonin promotes progesterone synthesis and supports the luteal phase; in the third trimester, it inhibits premature prolactin production to prevent preterm delivery [135, 138]. High melatonin levels in the third trimester aid in labor induction with oxytocin [139]. Melatonin may also affect early fetal development, influencing the development of the placenta, glia, and neurons [140]. Additionally, melatonin, as a non-toxic endogenous mediator, promotes cell proliferation, differentiation, and bone remodeling, and has anti-inflammatory, antibacterial, antioxidant, circadian rhythm regulation, and immune enhancement effects [141, 142]. The increased endogenous melatonin levels during pregnancy ensure normal pregnancy and fetal development and may regulate OTM by influencing bone deposition and resorption processes.

OTM relies on the coordinated absorption and remodeling of surrounding bone and periodontal tissue. The mechanical load applied to the tooth triggers an aseptic inflammatory response, leading to osteoclast activity in the compression area and osteoblast deposition in the tension area. Melatonin can promote the osteogenic differentiation of hPDLCs [143], increase the expression of inflammatory factors, and enhance collagen synthesis during mechanical strain [144]. Furthermore, melatonin directly stimulates osteoblast differentiation and proliferation, enhancing bone formation both in vitro and in vivo [145]. It can significantly inhibit local alveolar bone resorption and contribute to the healing of periodontal tissue [146].

Melatonin inhibits bone resorption in a number of different ways. Studies have shown that melatonin inhibits osteoclast differentiation and activation by increasing the OPG/RANKL ratio [147]. In addition to affecting PDLF, osteoblasts and osteoclasts, melatonin influences macrophage responses to mechanical strain. It converts macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, inhibiting inflammatory factor expression [148].

During orthodontic treatment, removable appliances are mainly worn at night, and the orthodontic force is transmitted to the teeth through these appliances. Increased melatonin secretion at night may affect macrophages exposed to mechanical strain, reducing their pro-inflammatory response and benefiting periodontal tissue repair during OTM [148]. In contrast to macrophages, melatonin enhances the mechanical strain-induced expression of inflammatory cytokines in PLFs, which

can compensate for the decreased cytokine production by macrophages in vivo [144]. Interestingly, studies have shown that although melatonin increases collagen synthesis and the expression of inflammatory mediators, it does not promote PDLF-induced osteoclast generation and cannot accelerate OTM [144]. This suggests that melatonin's mechanism in affecting OTM may not be related to inducing genes involved in bone remodeling through PLFs. As melatonin affects the entire body, it may also indirectly influence OTM or PLFs through other mediators not discussed in this paper. Research on melatonin's effect on OTM is still ongoing, with most studies limited to the cellular level. There is a lack of animal experiments to further verify melatonin's impact on OTM under orthodontic force.

Melatonin plays a crucial role in regulating bone metabolism and ensuring normal pregnancy and fetal development. In bone remodeling, melatonin up-regulates the expression of osteoblast proteins and down-regulates the production of osteoclasts. Additionally, melatonin influences the expression of inflammatory cytokines in macrophages, periodontal ligament cells (PDLCs), and PLFs. These cytokines are vital in regulating inflammatory responses and bone resorption. During pregnancy, the elevated levels of melatonin further impact bone metabolism, suggesting that melatonin may be involved in the regulation of OTM during pregnancy. However, there is currently a lack of evidence on how fluctuations in melatonin levels during pregnancy affect OTM and whether orthodontic treatment influences melatonin levels in the body. Given melatonin's importance in bone remodeling and pregnancy, future studies on its potential effects on OTM during pregnancy can better guide clinical assessments of the adverse side effects and risks of orthodontic treatment in pregnant women.

Effect of orthodontic treatment on hormone levels during pregnancy and lactation
Effect of orthodontic treatment on estrogen and progesterone levels during pregnancy
Hormonal changes during pregnancy can affect the rate of OTM by influencing bone metabolism. Concurrently, the application of orthodontic force impacts hormone levels during pregnancy. OTM promotes estrogen expression in the serum and local periodontal tissue of non-pregnant female rats [149, 150]. Although OTM increases estrogen levels in local tissues and the whole body, the overall rhythmic variation does not change [150]. However, during pregnancy, orthodontic force reduces progesterone secretion, with the most significant decrease occurring in the first trimester, followed by the third trimester, while still maintaining a gradual increase [75]. Similarly, microimplant loading (60 g) on the tibia

of pregnant mice down-regulates progesterone and estradiol expression [151].

Stress is a critical factor affecting the hypothalamic-pituitary-gonadal axis pathway. In non-pregnant female rats, orthodontic force increases estrogen levels [150], which seems inconsistent with findings that post-traumatic stress reduces hypothalamic-pituitary-gonadal axis activity [152]. The body's stress response is closely related to the endocrine environment during stress. The stress response induced by OTM in non-pregnant rats may be less severe [150]. The decrease in estrogen expression due to orthodontic force during pregnancy aligns with the reduced activity of the hypothalamic-pituitary-gonadal axis under stress, possibly due to a stronger stress response caused by orthodontic force during pregnancy.

Additionally, using orthodontic appliances increases TNF-α expression in the saliva of pregnant women [153], potentially affecting periodontal tissue health [154]. The use of various orthodontic appliances may hinder oral hygiene and exacerbate local inflammatory responses, altering local or systemic hormone levels. Existing research indicates that while corrective force during pregnancy affects hormone expression levels, the body compensates [151, 155]. Orthodontic treatment during pregnancy does not adversely affect the body but suggests that clinical caution is necessary.

Effect of orthodontic treatment on lactating estrogen level
The changes in hormone levels during lactation can regulate OTM, and the application of orthodontic force can also affect hormone levels in the body. Despite the reduction in estrogen secretion during lactation, orthodontic force can up-regulate serum estrogen levels, which promotes bone formation and helps mitigate the decrease in bone mineral density during this period, thus facilitating periodontal remodeling during lactation [7]. However, orthodontic force does not alter the overall pattern of estrogen changes during lactation, indicating that it does not interfere with the hypothalamus's regulation of estrogen rhythms but only affects estrogen content locally [7].

Orthodontic force increases serum estrogen content, possibly due to a systemic stress response, while the increase in local estrogen levels is directly related to periodontal remodeling from local stress [150]. A Study suggest that applying orthodontic force within a certain range during lactation is safe, as it accelerates OTM and reduces the risk of root resorption [77]. The decreased bone mineral density during lactation lowers resistance to tooth movement but increases anchorage requirements, necessitating careful control to avoid anchorage loss. Therefore, close monitoring, force adjustment, and enhanced anchorage control are essential in clinical practice during lactation.

Root resorption induced by orthodontic force is a multifactorial complication in orthodontic diagnosis and treatment, associated with the magnitude and direction of the force, individual differences, and hormone levels. OTM increases the risk of tooth root resorption [156]. Estrogen inhibits bone resorption and promotes osteogenic differentiation of bone marrow mesenchymal stem cells (MSCs) and PDLSCs, affecting the speed of tooth movement and root resorption [157]. Estrogen promotes cementoblast proliferation, differentiation, mineralization and cementum formation by regulating Notch signaling pathway [19]. In vitro studies have shown that estradiol can increase the proliferation rate of human cementoblasts by 2.5 times and promote new cementum formation [158]. Estrogen deficiency can increase the rate and extent of dental root resorption by cementoblasts [159, 77]. In experiments involving the application of force to the molars of rats, it was found that the OTM speed was accelerated in the ovariectomy group, and varying degrees of resorption pits were observed in the proximal and distal roots [77], indicating that reduced estrogen under pressure promotes orthodontic root resorption. Lactation is characterized by low estrogen levels, yet studies indicate that OTM accelerates and reduces the risk of root resorption during lactation, contrary to the increased risk of root resorption due to low estrogen levels [77]. It is hypothesized that the risk of orthodontic root resorption increases only when estrogen levels drop below a certain threshold, and the overall bone turnover and density decrease during lactation. Orthodontic force feedback is associated with increased estrogen expression [7].

Oral health maintenance during orthodontic treatment
During pregnancy, changes in the systemic and oral environment, diet, and oral hygiene habits of pregnant women increase the prevalence of oral diseases such as gingivitis, gingival hyperplasia, and pericoronitis of wisdom teeth [160]. Hormonal changes during pregnancy elevate the burden on periodontal tissues during orthodontic treatment, making it crucial to control inflammation during tooth movement to prevent tissue destruction, which can manifest as orthodontic-induced root resorption and periodontal disease [161]. Pregnancy gingivitis, the most common periodontal disease during pregnancy, results from the release of proinflammatory cytokines (including IL-6, IL-8, and IL-1β) due to increased progesterone and estrogen levels. Progesterone causes gingival capillary dilation and congestion, increases inflammatory cell and fluid exudation, exacerbating gingival inflammation caused by dental plaque. This hormonal effect enhances the gingival response to local irritants, worsening or altering the characteristics

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of pre-existing chronic gingival inflammation. Although histologically similar to gingivitis in non-pregnant individuals, gingivitis associated with hormonal changes during pregnancy is termed pregnancy gingivitis [162]. Gingival inflammation arises from both local and systemic factors; pregnancy is not the direct cause of gingivitis, but plaque microorganisms remain the primary cause of pregnancy gingivitis.

For patients undergoing orthodontic treatment during pregnancy, attention should be paid to both hormonal changes and oral inflammation. Neglecting oral hygiene and experiencing hormonal fluctuations during pregnancy often increase the incidence of oral diseases such as gingivitis. ERs are distributed in various tissues and are affected by hormone levels and oral hygiene, influencing the body's inflammatory state. During pregnancy, the expression of ERα in the maxillary sinus and periodontal membrane of rats is significantly increased, and slight inflammatory changes are observed in these tissues [155]. The use of various orthodontic appliances increases the difficulty of tooth cleaning and creates more conditions for plaque retention [163]. Although the use of fixed orthodontic devices alone may not cause gingivitis, factors such as pregnancy and poor oral hygiene can lead to gingivitis. Maintaining good oral hygiene can improve gingivitis during pregnancy, and severe gingivitis should be treated aggressively [164].

The second trimester is recognized as the safest period for oral treatment because fetal differentiation and development are mostly complete, tissues and organs are maturing, the risk of teratogenesis is low, and the pregnant woman's state of mind is stable [165, 166]. For pregnant patients without obvious contraindications, orthodontic revisit schedules are determined during the first and third trimesters, considering the actual situation of the pregnant woman and the fetus. In the latter half of the third trimester, chair-side operations should be shortened to avoid extreme supine positions, and complex and time-consuming treatments should be delayed until after delivery [167]. Ideally, tooth movement should not be performed during active gingival inflammation due to the increased risk of periodontal abscess formation [167]. For pregnant patients with signs of gingival inflammation, periodontal pocket formation, and poor oral hygiene, orthodontic treatment can exacerbate periodontal conditions, making it more sensible to postpone orthodontic treatment until after pregnancy. For patients with poor oral health who become pregnant during orthodontic treatment, it is recommended to terminate the treatment early and remove fixed appliances until the periodontal condition improves post-delivery.

Plaque control is crucial for orthodontic treatment during pregnancy. Before initiating orthodontics, existing periodontal problems must be addressed, and stringent oral hygiene maintenance should be implemented. This includes guidance on brushing, flossing, and using interdental cleaning tools, as well as professional periodontal treatment to remove local irritants and maintain optimal oral health [167]. Studies have reported that regular consumption of Lactobacillus reuteri lozenges is an effective adjunctive method to control pregnancy-related gingivitis [168]. Additionally, diet management and promoting oral health awareness play important roles in improving periodontal conditions during pregnancy.

Diet management

In addition to hormonal effects, adverse personal behaviors and changes in dietary habits exacerbate the deterioration of periodontal conditions during pregnancy [153]. Recent studies have shown that sweets and fast food can increase saliva acidity and affect the oral microbial composition, potentially promoting the growth of pathogenic bacteria [169, 170]. This underscores the need to focus on nutrition when improving the oral health of pregnant women. Dietary choices during pregnancy influence inflammatory processes, making nutrition a crucial factor in the systemic and oral health of both mother and child [171]. Nutritional deficiencies or snacking habits can lead to tooth decay, and excessive nutrient intake can cause overweight or obesity. Hormonal changes and rapid weight gain during pregnancy trigger metabolic inflammation, activating inflammatory processes throughout the body [172]. Weight gain or central obesity, influenced by diet and exercise, affects inflammatory conditions such as periodontitis [173], which is positively associated with increased IL-6 and TNF-α levels in the saliva of pregnant women with periodontitis [174]. Elevated TNF-α levels can affect infant weight [175], especially in obese pregnant women [176]. Meta-analysis by Shahi Anahita et al. [177] found that periodontal treatment could reduce the odds ratio of perinatal mortality and preterm birth by 88% and 31%, respectively. Active treatment of periodontal disease can effectively reduce the risk of adverse pregnancy outcomes. A reasonable diet, cultivation of good eating habits, and proper weight control during pregnancy can improve periodontal conditions and support orthodontic treatment.

Promote oral health awareness

Lack of awareness of oral care and weak social support are significant factors contributing to the deterioration of periodontal conditions during pregnancy [178]. Surveys indicate that pregnant women generally have low awareness of the importance of oral hygiene during pregnancy, and only a small number have an oral examination before or in the early stages of pregnancy [179]. This lack of awareness and understanding of the importance of oral health has become a self-neglect factor for

the worsening of periodontal conditions. Concerns about the safety of oral treatment during pregnancy, dental fear, and lack of awareness about the harm of oral diseases contribute to a low consultation rate for oral diseases among pregnant women [179]. Raising awareness of oral health care among pregnant women is crucial to avoid pregnancy-related adverse consequences due to gingivitis and periodontitis [180]. Additionally, women's oral health has been shown to deteriorate further in the postpartum period [167], increasing the difficulty and risk of OTM. While there are basic studies on changes in bone metabolism and OTM during pregnancy and lactation, reports on how orthodontists should conduct orthodontic treatment for this group of patients are lacking [181]. Periodontal health is essential for successful orthodontic treatment, and orthodontic care must consider the oral health of pregnant women. As the demand for dental services among pregnant women increases, promoting clinical standards for prenatal oral health to maximize coverage is becoming increasingly important [182]. However, social support remains weak, and deficiencies in knowledge and practice of oral health care during pregnancy persist among stomatologists [182]. Higher education institutions need to improve the teaching of oral treatment for pregnant women and raise awareness among stomatologists to disseminate knowledge of oral health care during pregnancy [183]. Preventive oral care should also be promoted as part of antenatal care. Strengthening interdisciplinary cooperation between obstetricians and stomatologists is recommended to improve the periodontal health of pregnant women, effectively identify risk factors for adverse pregnancy outcomes, and provide timely and effective interventions [184]. Overall, improving the awareness of oral health care among pregnant women is key, and only by enhancing self-awareness and professional oral maintenance can periodontal health be protected during orthodontic treatment.

Conclusion

Hormone levels are closely related to bone metabolism, and changes in bone homeostasis during pregnancy and breastfeeding may influence OTM trends. A review of previous studies indicates that orthodontic treatment during these periods should consider the effects of bone density reduction, force value, and interval of return visits. After applying orthodontic force, the body produces a stress response, causing hormone level fluctuations, but there are no reports of adverse effects. Additionally, most data in this review are based on rodent studies, which have certain limitations and cannot be directly extrapolated to humans. Despite differences between basic research and clinical practice, these findings should be approached with caution. Clinicians should be aware that

orthodontic patients may exhibit similar changes in bone remodeling during pregnancy or breastfeeding, which could have potential implications for clinical practice.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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