UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Wpływ zmiany stężenia hormonów podczas cyklu miesiączkowego na tempo przesunięć ortodontycznych

Effect of menstrual cycle hormone fluctuation on the rate of orthodontic movement

Rozprawa na stopień doktora nauk medycznych

Cykl publikacji powiązanych tematycznie

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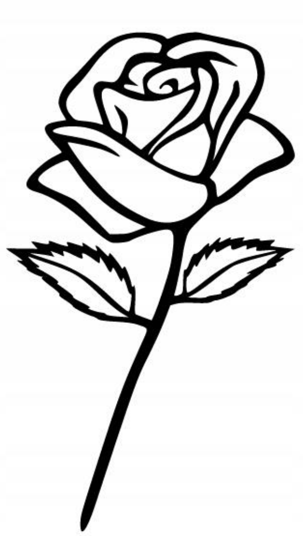

Spis treści

I. KRÓTKA CHARAKTERYSTYKA CYKLU PRAC STANOWIĄCYCH PODSTAWĘ ROZPRAWY DOKTORSKIEJ

Podstawę niniejszej rozprawy doktorskiej stanowi spójny tematycznie zbiór 4 artykułów opublikowanych w czasopismach naukowych, o łącznym **IF = 8,761**.

1. Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego.
2. Are currently selected laboratory animals useful in the research of how female hormones influence orthodontic biomechanics?
3. The impact of progesterone and estrogen on the tooth mobility.
4. Correlation of sex hormone levels with orthodontic tooth movement in the maxilla: a prospective cohort study.

Projekty badawcze uzyskały zgodę komisji bioetycznej (nr 788/2018), którą przedstawiłam w rozdziale VI niniejszej rozprawy.

Każde z badań prospektywno-obserwacyjnych przeprowadziłam pod opieką i nadzorem promotora.

Indywidualny wkład wszystkich autorów w powstanie każdego z artykułów stanowiących cykl niniejszej rozprawy opisałam w rozdziale VI.

II. STRESZCZENIE

1. Wstęp.

Współcześnie, ortodonci szukają możliwości przyspieszenia tempa przemieszczania zębów, ale ze zminimalizowaniem ryzyka występowania recesji dziąsła i resorpcji korzeni, czyli z wykorzystaniem procesów fizjologicznych zachodzących w organizmie, między innymi endokrynologicznych. Powszechnie wiadomo, że hormony systemowe, takie jak: estrogeny, androgeny i kalcytonina, prowadząc do wzrostu zarówno zawartości minerałów w kościach, jak i masy kostnej, powodują spowolnienie resorpcji kości, natomiast przyspieszają ją hormony tarczycy i kortykosteroidy. Nie ma jednak żadnych badań oryginalnych z udziałem kobiet, na temat tego, czy zmienny poziom progesteronu i estrogenów w cyklu miesiączkowym oraz stosowanie antykoncepcyjnych leków hormonalnych ma związek z rozciągnięciem lub naprężeniem więzadeł ozębnej (ang. Periodontal Ligaments, PDL) w trakcie leczenia ortodontycznego: głównymi procesami odpowiedzialnymi za przesuwanie zęba pod wpływem siły. Zdobycie jakościowych i ilościowych dowodów na wpływ hormonów kobiecych na PDL pozwoliłoby stworzyć protokół akceleracji ruchu zębów, ale z utrzymaniem równowagi, czyli bez negatywnych następstw resorpcji, która jest warunkiem *sine qua non* przemieszczeń zębów siłami ortodontycznymi.

2. Cel pracy.

Udowodnienie, że zmiany poziomu hormonów podczas cyklu miesiączkowego mogą istotnie wpływać zarówno na PDL, czyli na tempo przesuwania zębów, jak i na skuteczną profilaktykę chorób przyzębia po leczeniu ortodontycznym kobiet w wieku prokreacyjnym.

Cele pośrednie:

2.1. Poszukiwanie wyników badań dotyczących wpływu hormonów cyklu miesiączkowego na PDL,

2.2. Ocena jakości dowodowej wyników badań na zwierzętach doświadczalnych w aspekcie wpływu hormonów cyklu miesiączkowego na PDL u kobiet,
2.3. Ocena ruchomości zębów w różnych fazach cyklu miesiączkowego i podczas przyjmowania antykoncepcji hormonalnej,
2.4. Ocena ruchomości i tempa przemieszczania zębów po aktywacji aparatu ortodontycznego w różnych fazach cyklu miesiączkowego i podczas przyjmowania antykoncepcji hormonalnej.

3. Materiał i Metody.

3.1. Przegląd adekwatnego piśmiennictwa,
3.2. Krytyczna ocena wyników eksperymentalnych badań oryginalnych nad wpływem hormonów żeńskich, naturalnych lub egzogennych, których działanie zmienia tempo przemieszczania zębów: ewaluacja naukowa i moralna zasadności selekcji zwierząt oraz uzyskanych dowodów w aspekcie działania sił ortodontycznych u ludzi,
3.3. Ocena – za pomocą urządzenia Periotest – ruchomości zębów ludzkich w czasie cyklu miesiączkowego i podczas przyjmowania antykoncepcji hormonalnej. Do badań zakwalifikowano 60 kobiet w wieku 20-30 lat z mezjorotacją zębów 16 i 26. Grupę, odpowiednio: badaną i kontrolną, tworzyło 30 prawidłowo miesiączkujących pacjentek (M), podzielonych na trzy równoliczne podgrupy zależne od momentu cyklu, w którym przeprowadzano badanie: M1 (w fazie menstruacyjnej), M2 (w fazie owulacji) i M3 (w fazie lutealnej) oraz 30 pacjentek przyjmujących regularną antykoncepcję hormonalną, dwuskładnikową i jednofazową przez ponad 4 miesiące (S). Ruchomość zębów otrzymywano w jednostkach PTV (ang. Periotest Values, PTV): wzrost wartości oznaczał wzrost ruchomości zęba w zębodole,
3.4. Ocena ruchomości i tempa przemieszczania zębów ludzkich po aktywacji aparatu ortodontycznego w czasie cyklu miesiączkowego i podczas przyjmowania antykoncepcji hormonalnej. W tym celu badano skany porównawcze przed

aktywacją przerzutu podniebiennego (ang. Transpalatal Arch, TPA) i po jej dokonaniu. Badaniem objęto 120 pacjentek w wieku 20-30 lat z mezjorotacją zębów 16 i 26. Grupę badaną (A, n = 60) podzielono na trzy równoliczne podgrupy: A1 (w fazie menstruacyjnej), A2 (w fazie owulacji) i A3 (w fazie lutealnej); grupę kontrolną (B) stanowiły kobiety (n = 60) przyjmujące regularną antykoncepcję hormonalną, dwuskładnikową i jednofazową przez ponad 4 miesiące.

4. Wyniki.

4.1. Przegląd piśmiennictwa dowiódł, że wpływ cyklu miesiączkowego i hormonów jajnika na PDL był dotychczas badany jedynie u zwierząt,

4.2. Dokładna analiza badań, poparta wiedzą weterynaryjną wykazała, że żadna z dotychczasowych publikacji na temat związany z niniejszą rozprawą doktorską nie pozwala na ekstrapolację wyników na populację kobiet,

4.3. PTV mieściły się w granicach normy, ale kły i zęby trzonowe były zawsze stabilniejsze niż pozostałe. W grupie kobiet miesiączkujących (M) ruchomość zębów była statystycznie porównywalna w fazie menstruacyjnej (M1) i owulacyjnej (M2), a istotnie wzrosła w fazie lutealnej (M3). We wszystkich badaniach w grupie przyjmującej antykoncepcję hormonalną (S) omawiana ruchomość pozostawała stała i mniejsza niż w grupie M,

4.4. Tempo przemieszczania zębów po aktywacji aparatu ortodontycznego było istotnie różne w grupach badanych ($p < 0,001$), a najszybsze w podgrupie A3 (w fazie lutealnej).

5. Podsumowanie i wnioski.

Badanie wpływu poziomu żeńskich hormonów płciowych i dopuszczonych do użytku ogólnego doustnych środków antykoncepcyjnych na stabilność zębów w wyrostku zębodołowym oraz na skuteczność przemieszczeń ortodontycznych przeprowadzono po raz pierwszy u ludzi. Analizując badania eksperymentalne dowiedziono, że nie można ekstrapolować wyników zmian PDL zachodzących pod wpływem obciążenia u dotychczas wyselekcjonowanych zwierząt, na model ludzki, dlatego zaprojektowano badania z udziałem kobiet. Dzięki temu pokazano, że poziom omawianych hormonów jest istotnie skorelowany ze stabilnością zębów w wyrostku zębodołowym oraz ze skutecznością przemieszczeń ortodontycznych. ***Tym samym bezspornie dowiedziono, że u kobiet miesiączkujących aktywacji aparatu należy dokonywać w fazie lutealnej cyklu, w celu zwiększenia skuteczności leczenia ortodontycznego i ograniczenia jego powikłań, natomiast kobietom stosującym antykoncepcję hormonalną należy jeszcze przed rozpoczęciem terapii wytłumaczyć, że może ona spowalniać ruch zębów i wydłużyć czas leczenia***.

III. ABSTRACT

1. Introduction.

Nowadays, orthodontists are looking for opportunities to accelerate the pace of tooth movement, but while minimizing the risk of gingiva recession and root resorption, i.e. using physiological processes occurring in the body, including endocrine ones. It is well known that systemic hormones such as estrogens, androgens and calcitonin, by increasing both the mineral content in bones and bone mass, slow down bone resorption, while thyroid hormones and corticosteroids accelerate it. However, there are no original studies conducted in women on whether variable levels of progesterone and estrogen in the menstrual cycle and the use of hormonal contraceptives are related to the loosening or tightening of the periodontal ligaments (PDL) during orthodontic treatment: main processes responsible for tooth movement under the influence of force. Obtaining qualitative and quantitative evidence of the influence of female hormones on PDL would allow the creation of a protocol for the acceleration of tooth movement, but maintaining balance, i.e. without negative consequences of resorption, which is the sine qua non condition for tooth displacement by orthodontic forces.

2.Aim of the study

Proving that changes in hormone levels during the menstrual cycle can significantly affect both PDL, i.e. the rate of tooth movement, as well as effective prevention of periodontal diseases after orthodontic treatment in women of reproductive age.

Intermediate objectives:

2.1. Searching for research results regarding the influence of menstrual cycle hormones on PDL,

2.2. Assessment of the evidentiary quality of the results of studies on experimental animals as evidence in terms of the impact of menstrual cycle hormones on PDL,

2.3. Assessment of tooth mobility during the menstrual cycle and while taking hormonal contraception,

2.4. Assessment of the pace of tooth movement and their mobility after activation of the orthodontic appliance during the menstrual cycle and while taking hormonal contraception.

3. Material and Methods

3.1. Review of relevant literature,

3.2. Critical evaluation of the results of experimental original research on the influence of female hormones, natural or exogenous, whose action changes the rate of tooth movement: scientific and moral evaluation of the justification for animal selection and the obtained evidence in the aspect of the action of orthodontic forces in humans.

3.3. Assessment – using the Periotest device – of human tooth mobility during the menstrual cycle and while taking hormonal contraception. 60 women aged 20-30 with mesiorotation of teeth 16 and 26 were qualified for the study. The study and control groups, respectively, consisted of 30 normally menstruating patients (M), who were divided into three subgroups depending on the moment of the cycle in which the study was performed: M1 (in the menstrual phase), M2 (in the ovulation phase) and M3 (in the luteal phase) and 30 patients taking regular single-phase two-component hormonal contraception for more than 4 months (S). Tooth mobility was obtained in Periotest Values (PTV) units: an increase in the value meant an increase in tooth mobility in the alveolar.

3.4. Assessment of the rate of movement of human teeth after activation of the orthodontic appliance during the menstrual cycle and while taking hormonal contraception. For this purpose, comparative scans were examined before and after activation of the Transpalatal Arch (TPA). The study included 120 patients aged 20-30 with mesiorotation of teeth 16 and 26. The study group (A, n = 60) was divided into: A1 (in the menstrual phase), A2 (in the ovulation phase) and A3 (in the luteal phase) and a group control group (B, n = 60) taking regular two-component, single-phase hormonal contraception for more than 4 months.

4. Results.

4.1. A review of the literature showed that the influence of the menstrual cycle and ovarian hormones on PDL has so far only been studied in animals,

4.2. A thorough analysis of the research, supported by veterinary knowledge, has shown that none of the previous publications on the topic related to this doctoral dissertation allow for the extrapolation of the results to the female population,

4.3. PTVs were within normal limits, but canines and molars were always more stable than other teeth. In the group of menstruating women (M), tooth mobility was statistically comparable in the menstrual (M1) and ovulatory (M2) phases, and increased significantly in the luteal phase (M3). In all studies, mobility in the hormonal contraceptive group (S) remained constant and smaller than in the M group.

4.4. The rate of tooth movement after activation of the orthodontic appliance was significantly different in the study groups ($p < 0.001$), and the fastest in subgroup A3 (in the luteal phase).

5. Summary and conclusions.

The study of the influence of the level of female sex hormones and oral contraceptives approved for general use on the stability of teeth in the alveolar ridge and on the effectiveness of orthodontic relocations was carried out for the first time in humans. It was thus shown that the results of PDL changes from previous experimental studies in selected animals cannot be extrapolated to the human model. The study showed that the level of these hormones is significantly correlated with the stability of teeth in the alveolar process and with the effectiveness of orthodontic movements. Thanks to this, it has been indisputably proven that in menstruating women, the device should be activated in the luteal phase of the cycle in order to increase the effectiveness of orthodontic treatment and reduce its complications, while women using hormonal contraception should be explained before starting the therapy that it may slow down the movement of teeth and prolong the treatment time.

IV. SZCZEGÓŁOWA CHARAKTERYSTYKA PRAC STANOWIĄCYCH PODSTAWĘ ROZPRAWY DOKTORSKIEJ

IV.1.

Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego.

Charakterystyka. Przemieszczenie zębów pod wpływem sił ortodontycznych może ulegać spowolnieniu pod wpływem, między innymi: bisfosfonianów, metabolitów witaminy D, fluorków, leków przeciwzapalnych oraz sekrecji hormonów systemowych, takich jak estrogeny, androgeny i kalcytonina. Substancje te powodują wzrost zarówno zawartości minerałów w kościach, jak i masy kostnej oraz wolniejszą resorpcję kości. Przeciwnie, hormony tarczycy i kortykosteroidy mogą być sprawcami szybszego przesuwania zęba, przez co potencjalnie wpływają na mniej stabilny wynik leczenia ortodontycznego.

Praca dowiodła, że dotychczas nieznany jest wpływ progesteronu, estrogenów oraz antykoncepcyjnych leków hormonalnych na przemieszczanie zębów u człowieka, bo nie ma żadnych badań na ten temat. Wprawdzie oceny niestabilności więzadeł w czasie cyklu miesiączkowego dokonywano wielokrotnie, ale tylko w badaniach ortopedycznych i ginekologicznych zdrowych, młodych kobiet, a nie na poziomie stawu zębowo-zębodołowego, który ulega całkowitej przebudowie podczas terapii ortodontycznej. Wynik przeglądu doprowadził do realizacji pierwszego celu pośredniego pracy, czyli opisania teoretycznego wpływu ludzkich hormonów cyklu miesiączkowego na PDL podczas leczenia wad zgryzu.

IV.2.

Are currently selected laboratory animals useful in the research of how female hormones influence orthodontic biomechanics?

Charakterystyka. Zależność reakcji zębów na obciążenie siłami ortodontycznymi od poziomu hormonów żeńskich i antykoncepcji hormonalnej była przedmiotem badań wieloośrodkowych, prowadzonych na różnych gatunkach zwierząt. Większość testów wykonywano na białych szczurach Wistar stosowanych powszechnie w badaniach farmakologicznych, toksykologicznych, żywienia i testach behawioralnych; podobne badania przeprowadzono na królikach i kotach. Badania wykonywano albo na zdrowych samicach z własnym cyklem rujowym, albo na sterylizowanych, lub podawanych egzogennej stymulacji hormonalnej. Niektórym zwierzętom badano krew, innym śluz pochwowy. Przesuwano głównie kły, przedtrzonowce i siekacze. W tym celu zwykle stosowano otwarte sprężyny niklowo-tytanowe, a niekiedy zakotwienie kostne, czyli miniimplanty. Zakresy przemieszczeń mierzono na zębach gipsowych (wyciski pobierano w dniu badania) lub bezpośrednio u zwierzęcia, za pomocą suwmiarki. Po badaniach zwierzęta poddawano eutanazji. Realizacja drugiego celu pośredniego, czyli ocena jakości dowodowej wyników badań na zwierzętach doświadczalnych wykazała, że całkowita heterogenność zarówno uzębienia, jak i budowy ozębnej w porównaniu z populacją ludzką nie pozwala ekstrapolować wyników żadnych badań eksperymentalnych dotyczących związku poziomu hormonów z zachowaniami PDL, na pacjentów homo sapiens.

IV.3.

The impact of progesterone and estrogen on the tooth mobility.

Wstęp. Działanie estrogenów na tkanki przyzębia jest bezsporne. Hormony te regulują produkcję glikogenu nabłonkowego, redukują keratynizację dziąseł, a ostatecznie zmniejszają zarówno ochronną rolę bariery nabłonkowej, jak i reakcję limfocytów T, co prowadzi do zwiększonego występowania chorób dziąseł. Estrogeny stymulują także syntezę i dojrzewanie tkanek tworzących fibroblasty dziąsła oraz ich proliferację. Progesteron rozszerza łożyska naczyniowe, zwiększając ich przepuszczalność. Pobudza produkcję prostaglandyn i przyczynia się do wzrostu poziomu leukocytów wielojądrzastych, w przeciwieństwie do estrogenów. Progesteron utrudnia także syntezę kolagenu występującego w więzadłach przyzębia, co prowadzi do zmniejszenia zarówno ich potencjału do napraw, jak i liczby budujących je włókien; progesteron katalizuje metaboliczny rozkład kwasu foliowego niezbędnego do wzrostu, rozwoju i proliferacji komórek.

Z kolei nowoczesne antykoncepcyjne środki hormonalne mogą modyfikować odpowiedź immunologiczną, powodując ryzyko uszkodzenia układu odpornościowego przyzębia ze względu na zwiększenie zarówno liczby bakterii beztlenowych, jak i częstości występowania próchnicy.

Cel pracy. Ponieważ poziom omówionych hormonów istotnie wpływa na przyzębie utrzymujące ząb w zębodole, celem pracy była ocena ruchomości zębów w zależności od fazy cyklu miesiączkowego i podczas przyjmowania antykoncepcji hormonalnej.

Materiał i Metody. Badaniem prospektywnym, zgodnym z Deklaracją Helsińską objęto pacjentki w wieku 20-30 lat z mezjorotacją zębów 16 i 26. Grupę, odpowiednio, badaną i kontrolną tworzyło 30 pacjentek prawidłowo miesiączkujących (M) oraz 30 pacjentek przyjmujących regularną antykoncepcję hormonalną, dwuskładnikową i jednofazową przez ponad 4 miesiące w momencie rozpoczęcia badania (S). Badanie laboratoryjne krwi wraz z określeniem poziomu progesteronu i estrogenów oraz badanie ruchomości zęba przeprowadzono w trzech fazach cyklu miesiączkowego: menstruacyjnej (podgrupa M1), owulacji (podgrupa M2) i lutealnej (podgrupa M3) oraz w trzech terminach w grupie kontrolnej (S), z częstością równą badaniom podgrup.

Wyniki. W obu grupach poziom progesteronu i estrogenu mieścił się w normie właściwej dla fazy cyklu lub suplementacji hormonalnej. W podgrupach zaobserwowano istotną statystycznie różnicę w poziomach obu badanych hormonów ($p < 0,001$), co potwierdziło samodyscyplinę pacjentek zgłaszających się na badanie i rzetelność podziału jego uczestniczek. Wszystkie PTV mieściły się w granicach normy, jednak kły i zęby trzonowe zawsze były znacząco stabilniejsze niż pozostałe zęby, niezależnie od zarówno dnia cyklu miesiączkowego, jak i czasokresu stosowania środków antykoncepcyjnych. Ruchomość zębów była statystycznie porównywalna ($p > 0,05$) w podgrupie M1 i M2 i istotnie niższa ($p < 0,001$) niż w podgrupie M3. Zęby były tak samo ruchome ($p = 0,758$) u wszystkich badanych z grupy kontrolnej, niezależnie od terminu badania. PTV były znacząco wyższe u kobiet miesiączkujących (grupa M) niż u kobiet z grupy S, czyli ruchomość zębów w grupie M była większa ($p < 0,05$).

IV.4.

Correlation of sex hormone levels with orthodontic tooth movement in the maxilla: a prospective cohort study.

Cel pracy. W związku ze zdobyciem dowodów na wpływ hormonów cyklu miesiączkowego na PDL, celem pracy była ocena ruchomości i tempa przemieszczania zębów po aktywacji aparatu ortodontycznego, w zależności od fazy cyklu i podczas przyjmowania antykoncepcji hormonalnej.

Materiał i metody. Badaniem prospektywnym objęto pacjentki w wieku 20-30 lat z mezjorotacją zębów 16 i 26. Podzielono je na grupę badaną (A, n = 60) i kontrolną (B, n = 60), zachowując schemat z trzeciej pracy składającej się na cykl niniejszej dysertacji. Badano ruchomość wszystkich zębów szczęki (poza 17 i 27) oraz przemieszczenie zębów 16 i 26 po aktywacji TPA, której dokonywano za pomocą kleszczy Angle'a w taki sposób, aby uzyskać dystorotującą siłę ortodontyczną. Wolne końce TPA aktywowano pod kątem 45°, na podstawie kątomierza. Położenie zębów 16 i 26 przed aktywacją TPA i po jej dokonaniu rejestrowano za pomocą skanera. Na skanach wykonanych przed aktywacją (badanie 1) guzki policzkowe bliższe zębów 16 i 26 oznaczono, odpowiednio, jako mb16 i mb26, a odległość między nimi w linii prostej (mm), jako szerokość międzytrzonowcową (ang.: Intemolar Width, IMW1). Po aktywacji oceniano ruchomość zębów 16 i 26 za pomocą Periotestu. Położenie punktów mb16 i mb26 na skanach wykonanych 6 tygodni po aktywacji TPA (badanie 2) oznaczano jako mb16' i mb26' oraz mierzono nową szerokość międzytrzonowcową IMW2. Następnie skany z badania 1 i 2 nakładano wzdłuż środka przednio-tylnej bruzdy centralnej zębów 16 i 26 w celu pomiaru zarówno odrotowania zębów 16 (O16 = mb16' – mb16) i 26 (O26 = mb26' – mb26), jak i wzrostu szerokości międzytrzonowej (IMW2-IMW1) w wyniku działania TPA.

Wyniki. Ruchomość pierwszych zębów przedtrzonowych, kłów i siekaczy była podobna (p = 0,57), poza podgrupą A3, w której zaobserwowano większą ruchomość zębów 14 i 24. Wartości PTV1 i PTV2, IMW1 i IMW2 oraz O16 i O26 różniły się w zależności od grupy. W wyniku działania TPA doszło do przesunięcia zębów 16 i 26 u wszystkich badanych kobiet, ale było ono najmniejsze i podobne w podgrupie A2 i B (p = 0,64). Wartości wymienionych parametrów w podgrupie A1 były istotnie wyższe niż w grupie B (p < 0,001), ale też istotnie niższe niż w podgrupie A3 (p < 0,001). Dowiodło to, że najlepszą skuteczność TPA uzyskuje się aktywując go w lutealnej fazie cyklu miesiączkowego.

Podsumowanie i wnioski.

Ponieważ badań stanowiących podstawę niniejszej rozprawy nigdy nie przeprowadzono z udziałem kobiet, podczas pozyskiwania ewidencji oceniano rezultaty uzyskane w wielu eksperymentach przeprowadzonych na różnych gatunkach zwierząt laboratoryjnych. Szybko jednak ustalono, że heterogenność materiału (w porównaniu z populacją ludzką), w połączeniu z faktem, iż badania na modelach zwierzęcych nie są długoterminowe, czyli mało wiarygodne naukowo, stanowi ich poważne ograniczenie. Nie oznacza to rzecz jasna rekomendacji *„reductio ad absurdum"* badań na zwierzętach w medycynie. Niemniej, powinno zachęcać do staranniejszej selekcji gatunków zwierząt do badań eksperymentalnych.

W wyniku zdobycia powyższych materiałów dowodowych zaprojektowano badania oryginalne z udziałem populacji kobiet, zgodne z zasadami bioetyki. Na podstawie ilościowych i jakościowych ocen zmian ruchomości zębów i tempa ich przemieszczenia w wyniku leczenia ortodontycznego dowiedziono, że obie te zmienne są istotnie zależne od poziomu żeńskich hormonów płciowych.

Reasumując, zaprezentowane wyniki dysertacji wykazały, że leczenie ortodontyczne młodych kobiet powinien poprzedzać wywiad zawierający, między innymi, informację na temat cyklu menstruacyjnego. Dzięki temu można wyjaśnić pacjentkom stosującym antykoncepcję, dlaczego spowalnia ona ruch zębów i wydłuża czas leczenia ortodontycznego. Przede wszystkim jednak można wybrać ***optymalny moment aktywacji aparatu ortodontycznego, który u kobiet miesiączkujących powinien następować w fazie lutealnej cyklu miesiączkowego, w celu zarówno zwiększenia skuteczności terapii wad zgryzu, jak i ograniczenia jej powikłań w postaci jatrogennych resorpcji***.

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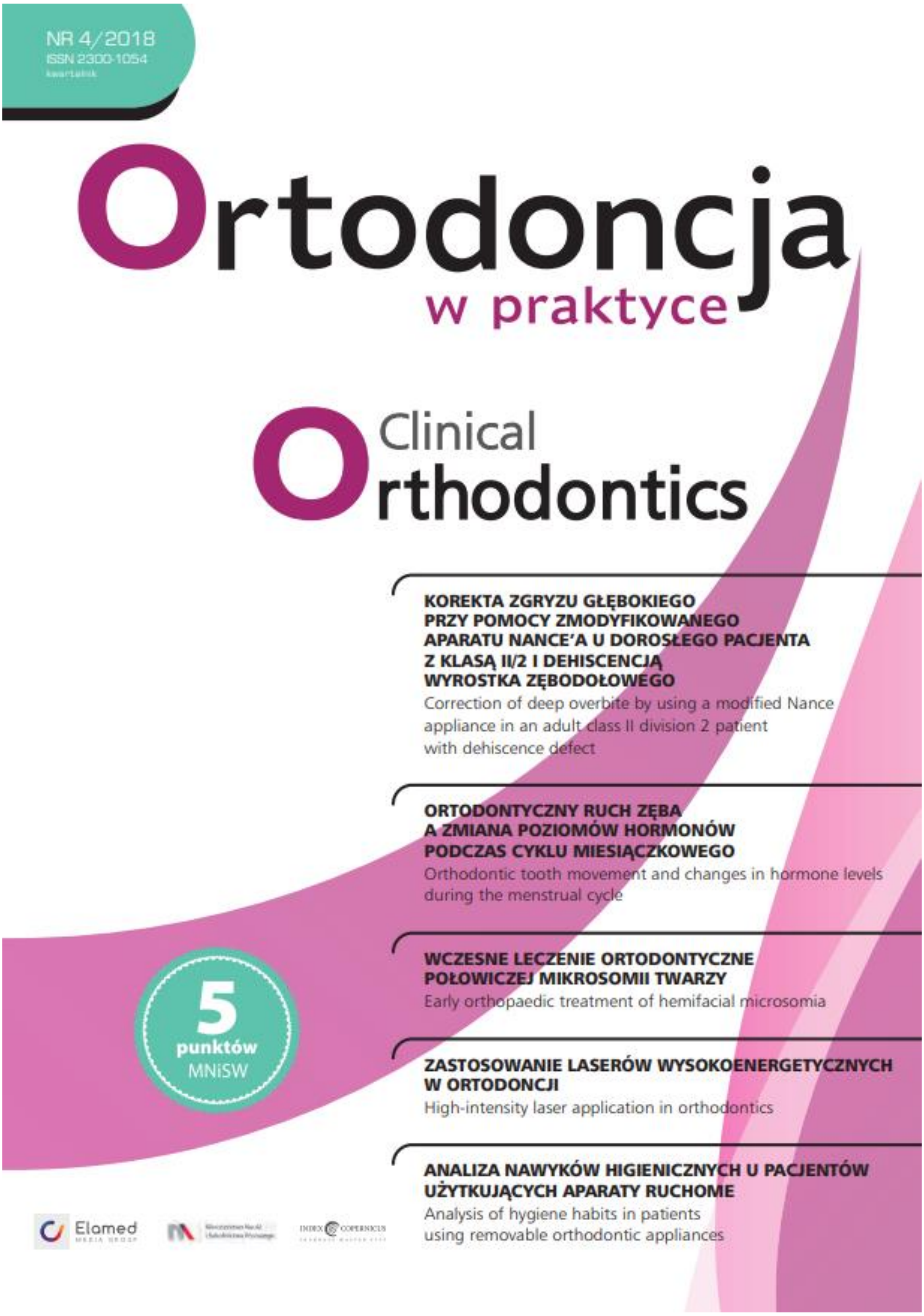
VI. ZAŁĄCZNIKI

1. Kopie opublikowanych artykułów wchodzących w skład rozprawy doktorskiej.



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Ortodoncja w praktyce

Clinical Orthodontics

KOREKTA ZGRYZU GŁĘBOKIEGO PRZY POMOCY ZMODYFIKOWANEGO APARATU NANCE'A U DOROSŁEGO PACJENTA Z KLASĄ II/2 I DEHISCENCJĄ WYROSTKA ZĘBODOŁOWEGO
Correction of deep overbite by using a modified Nance appliance in an adult class II division 2 patient with dehiscence defect

ORTODONTYCZNY RUCH ZĘBA A ZMIANA POZIOMÓW HORMONÓW PODCZAS CYKLU MIESIĄCZKOWEGO
Orthodontic tooth movement and changes in hormone levels during the menstrual cycle

WCZESNE LECZENIE ORTODONTYCZNE POŁOWICZEJ MIKROSOMII TWARZY
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High-intensity laser application in orthodontics

ANALIZA NAWYKÓW HIGIENICZNYCH U PACJENTÓW UŻYTKUJĄCYCH APARATY RUCHOME
Analysis of hygiene habits in patients using removable orthodontic appliances

5 punktów MNiSW

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Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego

Orthodontic tooth movement and changes in hormone levels during the menstrual cycle

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Ruch zęba następuje m.in. w wyniku przyłożenia siły generowanej przez aparat ortodontyczny. Ruch ten składa się z trzech etapów: początkowego przechylenia, fazy opóźnienia i progresywnego ruchu zęba. W fazie pierwszej więzadła ozębnej (ang. *periodontal ligament* – PDL) są ściskane w sąsiedztwie kości wyrostka zębodołowego po stronie, w którą skierowana jest siła. Po przeciwnej stronie więzadła ozębnej wydłużają się i napinają. Po fazie początkowego przechylenia następuje faza opóźnienia,

Tooth movement occurs among others as a result of applying force generated by orthodontic appliances. This movement consists of three stages: initial tipping, lag phase and progressive tooth movement. In the first phase, the periodontal ligament (PDL) is squeezed in the vicinity of the alveolar bone on the side to which the force is directed. On the opposite side, periodontal ligaments stretch and tense. After the initial tipping phase, there is a lag phase, i.e. cell mobilization,

Słowa kluczowe:
ortodoncja, układ hormonalny, cykl miesiączkowy, więzadła przyzębia, metabolizm kości
Keywords:
orthodontics, endocrine system, menstrual cycle, periodontium ligaments, bone metabolism

Streszczenie: Ortodontyczny ruch zęba wynika z reakcji tkanek przyzębia na przykładane siły mechaniczne, co prowadzi do przemodelowania lub przebudowy kości zębodołu. Wiadomo jednak, że opisywane przemieszczenie nie zależy tylko od samej siły, ale i – między innymi – od układu wewnątrzwydzielniczego. Szczególnym przykładem jego działania są zmiany poziomu hormonów w cyklu miesiączkowym. Hormony te, ze względu na wpływ na metabolizm kostny i więzadła, mogą mieć związek z tempem przesunięć zębowych. Analiza tej tezy była celem niniejszej pracy służącej pogłębieniu wiedzy o leczeniu ortodontycznym pacjentek w wieku prokreacyjnym.

Summary: Orthodontic tooth movement results from the reaction of periodontal tissues to applied mechanical forces, leading to remodeling or reconstruction of the alveolar bone. It is known, however, that the described movement does not depend only on the force itself, but also – among others – on the endocrine system. A special example of its action involves changes in hormone levels in the menstrual cycle. These hormones, due to their influence on bone metabolism and ligaments, may be related to the rate of tooth movement. The analysis of this thesis was the purpose of this study, aimed at deepening the knowledge about orthodontic treatment of female patients at the procreative age.

czyli mobilizacja komórek, która pozwoli na przebudowę PDL i kości dzięki osteoklastom i osteoblastom. Długość tej fazy zależy częściowo od zastosowanej siły: jej przedawkowanie powoduje, że korzeń zbliża się nadmiernie do ścianki zębodołu. Następuje wówczas zamknięcie naczyń krwionośnych, a ruch zęba ulegnie spowolnieniu. Ten etap może trwać od kilku dni do kilku tygodni. Faza końcowa charakteryzuje się faktyczną przebudową kości polegającą na apozycji w obszarach napięcia i resorpcji w obszarach kompresji. Proces ten skutkuje przesuwaniem zęba [1-8].

Opisane zjawiska zachodzące podczas leczenia ortodontycznego zależą nie tylko od samej siły. Nie bez wpływu są m.in.: jakość pożywienia, zaburzenia metaboliczne wywołujące choroby kości, wiek pacjentów czy też przyjmowane przez nich lekarstwa. W różnych badaniach wykazano, że leki, takie jak: bisfosfoniany, metabolity witaminy D czy fluorki, hipotetycznie powodują spowolnienie ruchu zębów, podobnie jak niesteroidowe leki przeciwzapalne, które zmniejszają resorpcję kości. Długotrwałe stosowanie tych substancji może zatem opóźnić odpowiedź osteoklastów, niezbędną do przesunięcia zębów pod wpływem przyłożonej siły [9, 10].

Nie sposób w tym wachlarzu czynników pominąć działania hormonów, które – wpływając na więzadła stawu zębowo-zębodołowego czy też metabolizm kostny – mogą istotnie moderować tempo przemieszczeń zębów. Sekrecja hormonów, takich jak: estrogeny, androgeny i kalcytonina, powoduje wzrost zarówno zawartości minerałów w kościach, jak i masy kostnej oraz spowolnienie resorpcji kości, co może opóźnić ruch ortodontyczny zęba. Przeciwnie, hormony tarczycy i kortykosteroidy mogą przyspieszać tempo przesuwania zęba, przez co potencjalnie wpływają na mniej stabilny wynik po leczeniu ortodontycznym [9, 10].

Współczesny wzrost zainteresowania leczeniem ortodontycznym wśród młodych dorosłych kobiet – w wieku od 20 do 30 lat – jest w naturalny sposób powiązany z sekrecją hormonów jajnika. Powstaje zatem pytanie, czy tempo uzyskania prawidłowej okluzji i kosmetycznej poprawy uśmiechu, których oczekują pacjentki, może być zależne od różnych faz cyklu miesiączkowego i wydzielanych przez jajniki hormonów.

Cykl miesiączkowy i hormony jajnika wpływające na układ kostny oraz grę naczyniową

Cykl miesiączkowy jest korelacją trzech różnych sprzężeń zwrotnych: podwzgórzowo- przysadkowego, jajnikowego oraz endometrialnego. Nadrzędny jest układ podwzgórze – przysadka. Składają się na niego trzy pętle. Pierwsza, tzw. ultrakrótka, jest uzależniona od podwzgórza. Wydzielana przez nie pulsacyjnie gonadoliberyna (GnRH) powoduje sprzężenie zwrotne w wyniku zmiany stężenia hormonu w komórkach. Kolejna pętla, nazywana krótką, jest zależna od przysadki mózgowej. Jej przedni płat wydziela – pod

which allows for the reconstruction of PDLs and bones, thanks to osteoclasts and osteoblasts. The duration of this phase depends partly on the force applied: its overdose causes the root to approach to the alveolar wall excessively. Then, the blood vessels are closed and tooth movement will slow down. This phase can last from several days to several weeks. The final phase is characterized by actual bone remodeling, consisting in apposition in the areas of tension and resorption in the areas of compression. This process results in tooth movement [1-8].

The phenomena described occurring during orthodontic treatment depend not only on the force applied. Among others, quality of food, metabolic disorders that cause bone diseases, patients' age, and medications taken by them are also important. Various studies have shown that medications such as bisphosphonates, vitamin D metabolites or fluorides hypothetically cause that tooth movement is slowed down, as do non-steroidal anti-inflammatory drugs that reduce bone resorption. Long-term use of these substances may therefore delay the osteoclast response necessary to move teeth under the influence of the applied force [9, 10].

It is impossible to leave out the influence of hormones in this range of factors, which – affecting the ligaments of the dental-alveolar joint or bone metabolism – can significantly moderate the rate of tooth movement. The secretion of hormones, such as estrogens, androgens and calcitonin, increases bone mineral content as well as bone mass and it slows bone resorption, which may delay orthodontic tooth movement. On the contrary, thyroid hormones and corticosteroids can accelerate the rate of tooth movement, thus potentially affecting the less stable outcome after orthodontic treatment [9, 10].

The current increase in the interest in orthodontic treatment among young adult women – 20 to 30 years old – is naturally related to the secretion of ovarian hormones. Hence, a question arises: can the rate of correct occlusion and cosmetic improvement of the smile expected by patients be dependent on the various phases of the menstrual cycle and hormones secreted by the ovaries?

Menstrual cycle and ovarian hormones affecting the skeletal system and vessel peristalsis

The menstrual cycle constitutes a correlation of three different feedbacks: hypothalamohypophyseal, ovarian and endometrial. The hypothalamohypophyseal complex is the supreme one. It consists of three loops. The first one – the so-called ultra-short loop – depends on the hypothalamus. Gonadoliberin (GnRH), secreted in pulses, causes the feedback due to changes in the hormone concentration in cells. The next loop – the called the short one – depends on the pituitary gland. Its frontal lobe secretes – under the influence of GnRH – lutropin (LH) and follicle stimulating hormone (FSH), which inhibit the wpływem GnRH – lutropinę (LH) i folikulotropinę (FSH), które hamują zwrotnie czynność podwzgórza. Ostatnia pętla, nazywana długą, jest utworzona przez sprzężenie zwrotne między hormonalną czynnością jajników a podwzgórza i przysadki [11-15].

Cykl jajnikowy składa się z trzech faz. Pierwszą jest faza folikularna. Rozpoczyna się ona od stymulowanego przez FSH przekształcenia pęcherzyków pierwotnych w pęcherzyki preantralne, po czym dokonuje się rozwój komórki jajowej, osłonki przejrzystej i komórek ziarnistych produkujących estrogeny. Następnie FSH wraz z estrogenami powoduje przekształcenie pęcherzyków preantralnych w pęcherzyki antralne. Poprzez selekcję tworzy się pęcherzyk dominujący, który zaczyna wydzielać estradiol, co – przez sprzężenie zwrotne – skutkuje spadkiem FSH. Wpływa to na zahamowanie wzrostu innych pęcherzyków. Pęcherzyk dominujący jest przekształcany w pęcherzyk przedowulacyjny, co wzmaga jeszcze bardziej wydzielanie estrogenów, a to – poprzez sprzężenie zwrotne dodatnie – wpływa na wzrost wydzielania LH. Równocześnie inicjowany jest proces luteinizacji i następuje produkcja progesteronu i inhibiny. Szczyt wydzielania estrogenów zachodzi na 24-36 godziny przed owulacją. Na tę pierwszą fazę jajnikową przypadają dwie pierwsze fazy cyklu endometrialnego: miesiączkowa i proliferacyjna. Faza miesiączkowa zaczyna się krwawieniem wynikającym ze złuszczenia warstwy czynnościowej błony śluzowej macicy. Kończy się po 5 dniach i przechodzi płynnie w fazę proliferacyjną, która jest ściśle związana z różnicowaniem się pęcherzyka przedowulacyjnego. Czas fazy proliferacyjnej jest zmienny, jednak określa się, że fizjologicznie trwa od 7 do 13 dni. Następnie w cyklu jajnikowym występuje owulacja, a w cyklu endometrialnym – faza owulacyjna. Wynikają one ze wzrostu poziomu LH i estrogenów. Pod wpływem progesteronu następuje destabilizacja ściany pęcherzyka. Złożone działanie FSH, LH i progesteronu wpływa na aktywację enzymów proteolitycznych i podwyższenie stężenia prostaglandyn w płynie pęcherzykowym oraz wzrost ciśnienia w pęcherzyku Graafa, co powoduje jego pęknięcie i uwolnienie oocytu. Faza trwa 24 godziny i jest najkrótsza. W cyklu jajnikowym następuje faza lutealna wynikająca z intensywnej waskularyzacji ciałka żółtego. Szczyt przypada na 8. i 9. dzień od owulacji, koreluje to też ze wzrostem wydzielania progesteronu. Około 10.-11. dnia od owulacji rozpoczyna się regresja ciałka żółtego. Faza lutealna trwa 13-15 dni (przeciętnie 14). W tym czasie w cyklu endometrialnym trwa 14-dniowa faza sekrecyjna. Pod wpływem progesteronu następuje pogrubienie błony śluzowej macicy, która jest źródłem wielu substancji, takich jak: relaksyna, endorfina, czynniki wzrostu śródbłonka naczyniowego, transformujący czynnik wzrostu oraz lipidy i interleukiny. Faza owulacji i faza lutealna są stałe, fizjologiczna długość cyklu wynosi średnio 28 dni, a jej skrócenie do 24 dni lub wydłużenie do 35 dni zależy od pierwszej fazy [11-15].

hypothalamus function. The last loop – called the long one – is formed by the feedback between the hormonal activity of the ovaries and the hypothalamus and pituitary [11-15].

The ovarian cycle consists of three phases. The first one is the follicular phase. It starts with the transformation of primary vesicles into preantral follicles stimulated by FSH, followed by the development of the ovum, the transparent membrane, and estrogen-producing granulosa cells. Next, FSH together with estrogens causes the transformation of preantral follicles into antral follicles. By selection, a dominant follicle is formed, which begins to secrete estradiol, which – by feedback – results in a decrease in FSH. This affects the inhibition of growth of other follicles. The dominant follicle is transformed into the preovulatory follicle, which further enhances the secretion of estrogens, and this – through positive feedback – affects the growth of LH secretion. At the same time, the process of luteinization is initiated and progesterone and inhibin are produced. The peak of estrogen secretion occurs 24-36 hours before ovulation. This first ovarian phase is divided into the first two phases of the endometrial cycle: menstrual and proliferative. The menstrual phase begins with bleeding resulting from the exfoliation of the functional layer of the uterine mucosa. It ends after 5 days and passes smoothly to the proliferative phase, which is closely related to the differentiation of the preovulatory follicle. The duration of the proliferative phase is variable, but it is determined that physiologically it lasts for 7 to 13 days. Then, in the ovarian cycle ovulation takes place, and in the endometrial cycle – the ovulation phase. They result from an increase in the level of LH and estrogens. Under the influence of progesterone, the follicular wall is destabilized. The combined action of FSH, LH and progesterone affects the activation of proteolytic enzymes, and increases the concentration of prostaglandins in the follicular fluid and pressure in the Graafian follicle, which causes its rupture and release of the oocyte. The phase lasts 24 hours and is the shortest one. Within the ovarian cycle the luteal phase occurs resulting from intensive vascularisation of the corpus luteum. The peak falls on the 8th and 9th day of ovulation, it also correlates with the increase in progesterone secretion. About 10-11 days after the ovulation regression of the corpus luteum begins. The luteal phase lasts 13-15 days (14 on average). During this time, the endometrial cycle involves a 14-day secretion phase. Under the influence of progesterone, thickening of the endometrium occurs, which is the source of many substances, such as: relaxin, endorphin, vascular endothelial growth factors, transforming growth factors and lipids and interleukins. The ovulation phase and the luteal phase are constant; the physiological cycle length is 28 days on average, and its reduction to 24 days or the extension to 35 days depends on the first phase [11-15].

Hormonami jajników wpływającymi na metabolizm kości oraz grę naczyniową prowadzącą do relaksacji więzadeł są hormony steroidowe: estradiol i progesteron, oraz hormon peptydowy – relaksyna. Przedstawiciel estrogenów, czyli 17-beta-estradiol to hormon, którego wydzielanie odbywa się przez komórki ziarniste pęcherzyka jajnikowego, począwszy od menarche (pierwsza miesiączka), aż do menopauzy (ostatnia miesiączka). Odgrywa on istotną rolę w regulacji cyklu miesiączkowego. Estrogeny są uważane za najważniejsze hormony wpływające na metabolizm kości u kobiet. Hamują wytwarzanie różnych cytokin powodujących resorpcję kości, stymulują organizm do tworzenia osteoblastów oraz hamują reakcję tych ostatnich na parathormon. Nie mają żadnego działania anabolicznego na tkankę kostną. Stymulują bezpośrednio aktywność kościotwórczą osteoblastów i wpływają na wzrost liczby receptorów witaminy D3, dlatego też hipoestrogenizm powoduje osteoporozę, która jest częsta u kobiet po menopauzie [11-15].

Progesteron należy do grupy gestagenów. Stymuluje rozrost endometrium, ułatwiając zagnieżdżenie się zarodka. Poza wpływem na narządy rozrodcze działa również na cały organizm. Hamuje odpowiedź immunologiczną na antygeny, jest substratem do produkcji kortykosteroidów i mineralokortykoidów. Powoduje także zwiększenie łożyska naczyniowego poprzez rozszerzenie żył i spowolnienie przepływu krwi [11-15].

Relaksyna to znany od dziesięcioleci hormon ciążowy, ale wydzielany także w nieznacznych ilościach tuż przed miesiączką. Produkowany jest przez ciałko żółte jajnika i błonę śluzową macicy. Wykazano, że ma on wpływ na wiele innych procesów fizjologicznych zachodzących w organizmie kobiety, m.in. na: grę naczyniowo-ruchową, osmolalność osocza, angiogenezę oraz metabolizm kolagenu [11-15].

Jak wynika z przedstawionego tu mechanizmu działania wydzielanych w czasie cyklu miesiączkowego hormonów jajnika, ich wpływ na tempo ruchu zębów pod wpływem siły ortodontycznej wydaje się bardzo prawdopodobny. Mimo to w polskim piśmiennictwie naukowym nigdy nie podjęto tego zagadnienia.

Dyskusja

Większość opisanych w literaturze zagranicznej badań dotyczących związku tempa przesuwania zębów za pomocą aparatów ortodontycznych z działaniem hormonów wydzielanych podczas menstruacji przeprowadzono na zwierzętach, którym podawano ludzki progesteron, estrogen i relaksynę [16-18]. Jeżeli chodzi o progesteron, to badania eksperymentalne na szczurach przeprowadzone przez zagranicznych autorów dowiodły, że hormon ten modyfikuje ruch ortodontyczny zębów, poprzez wpływ na przyzębie i na sprężystość blaszki kostnej wyrostka zębodołowego. Z kolei długotrwałe podawanie progesteronu królikom spowodowało zmniejszenie szybkości porusza-

Ovarian hormones that affect bone metabolism and vessel peristalsis leading to relaxation of the ligaments are steroid hormones: estradiol and progesterone, and peptide hormone – relaxin. An estrogen representative, i.e. 17-beta-estradiol, is a hormone the secretion of which takes place through granulosa cells of the ovarian follicle, beginning with menarche (the first menstruation) up to menopause (the last menstrual period). It plays an important role in regulating the menstrual cycle. Estrogens are considered the most important hormones affecting bone metabolism in women. They inhibit production of various cytokines that cause bone resorption, stimulate the body to form osteoblasts and inhibit the latter's response to parathyroid hormone. They have no anabolic effect on bone tissue. They directly stimulate osteoblasts' osteogenic activity and increase the number of vitamin D3 receptors, which is why hypoestrogenism causes osteoporosis, which is common in postmenopausal women [11-15].

Progesterone belongs to the group of gestagens. It stimulates growth of the endometrium, facilitating the implantation of the embryo. In addition to the effects on reproductive organs, it also works on the whole body. It inhibits the immune response to antigens, is a substrate for the production of corticosteroids and mineralocorticoids. It also increases the vascular bed by expanding veins and slowing down the blood flow [11-15].

Relaxin is a pregnancy hormone that has been known for decades, but it is also secreted in small quantities just before menstruation. It is produced by the corpus luteum of the ovary and the endometrium. It has been shown that it affects many other physiological processes taking place in a woman's body, among other vessel and motor peristalsis, plasma osmolality, angiogenesis and collagen metabolism [11-15].

As evidenced by the mechanism of action of ovarian hormones secreted during the menstrual cycle, their impact on the rate of tooth movement under the influence of orthodontic force seems very likely. Nevertheless, this subject has never been addressed in Polish scientific literature.

Discussion

The majority of studies described in foreign literature on the relationship between the rate of tooth movement with orthodontic appliances and the effects of hormones secreted during menstruation were carried out on animals administered with human progesterone, estrogen and relaxin [16-18]. As for progesterone, experimental studies on rats conducted by foreign authors have shown that this hormone modifies orthodontic tooth movement, through the effect on the periodontium and the elasticity of the alveolar bone plate. On the other hand, prolonged administration of progesterone to rabbits caused a decrease in the rate of tooth movement; the authors nia się zęba; autorzy uznali, że powodem mógł być fakt, że osteoklasty obserwowane są głównie 2 dni po zastosowaniu siły ortodontycznej [11-16]. Co do relaksyny, to w literaturze istnieją wyniki badań – również eksperymentalnych – które dowodzą, że podanie relaksyny szczurom i psom powoduje przyspieszenie ortodontycznego ruchu zębów w porównaniu do grup kontrolnych, a także – rozciągnięcie utworzonej z tkanki miękkiej ozębnej u szczurów [11-15, 17, 19-22].

Temat niestabilności więzadeł w czasie cyklu miesiączkowego był wprawdzie wielokrotnie poruszany w badaniach na ludziach, ale jedynie w medycynie ogólnej. Badania przeprowadzono na zdrowych, młodych kobietach. Lekarze zauważyli wpływ estrogenu i progesteronu na mniejszą stabilność więzadeł stawu kolanowego oraz stawu skokowego, dowodząc tym samym zwiększonego ryzyka kontuzji tych stawów w czasie cyklu miesiączkowego [23]. Podobne badania prowadzili lekarze ginekolodzy u ciężarnych kobiet, u których stwierdzili zwiększoną pod wpływem tych dwóch hormonów mobilność więzadeł spojenia łonowego [24].

Mimo udokumentowanego wpływu hormonów cyklu miesiączkowego na kość i więzadła ludzkie, nie ma jednoznacznej ewidencji dotyczącej związku tych substancji z tempem ruchu zębów w wyrostku zębodołowym. Zagadnienie to jest bardzo ważne, bowiem dziś gabinety ortodontyczne odwiedzane są przez pacjentów dorosłych, których gro stanowią kobiety między 20. a 30. rokiem życia, czyli w wieku prokreacyjnym. Główną przyczyną zgłaszania się takich pacjentek do ortodonty jest niezadowolenie z uśmiechu lub rysów twarzy, bowiem właśnie wtedy wzrasta u kobiet świadomość swojego ciała. Łatwiej jest też im decydować o sobie, gdyż zarabiają, a więc mają własne dochody, które mogą poświęcić na dbanie o swój wygląd. Pacjentki te oczekują również jak najszybszego efektu leczenia nieprawidłowej okluzji. Co istotne – u kobiet pomiędzy 20. a 30. rokiem życia stabilizuje się gospodarka hormonalna, rozchwiana okresem dojrzewania. I skoro hormony cyklu miesiączkowego zaczynają odgrywać stałą, ale jednoznaczną rolę w organizmie, wypełnienie luki w nauce dotyczącej ich powiązania z tempem przesuwania zębów pod wpływem leczenia ortodontycznego wydaje się nieodzowne.

Podsumowanie

Pogłębienie wiedzy na temat wpływu cyklu miesiączkowego, a tym samym hormonów jajnika na zwiotczenie więzadeł stawu zębowo-zębodołowego i na sprężystość wyrostka zębodołowego może w przyszłości pozwolić na skuteczniejszą profilaktykę chorób przyzębia po leczeniu ortodontycznym oraz na określenie najlepszej metody przyspieszenia ruchu zęba pod wpływem siły ortodontycznej.

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concluded that this could be caused by the fact that osteoclasts are observed mainly 2 days after the application of the orthodontic force [11-16]. As for relaxin, literature provides results of studies – also experimental – that prove that administering relaxin to rats and dogs accelerates orthodontic tooth movement compared to control groups; it also accelerates stretching of soft periodontal tissue formed in rats [11-15, 17, 19-22].

The subject of instability of ligaments during the menstrual cycle has been repeatedly discussed in human studies, but only in general medicine. Studies were carried out on healthy young women. Doctors noticed the effect of estrogen and progesterone on lower stability of knee ligaments and ankle joints, thus proving the increased risk of injury to these joints during the menstrual cycle [23]. Similar studies were carried out by gynecologists in pregnant women in whom it was found that mobility of pubic symphysis was increased under the influence of these two hormones [24].

Despite the documented influence of hormones of the menstrual cycle on the bones and human ligaments, there is no unambiguous record regarding the relationship of these substances with the rate of tooth movement in the alveolus. This issue is very important, because today orthodontic clinics are visited by adult patients, including women between 20 and 30 years of age, that is at their procreative age. The main reason for such patients to come to orthodontists is their dissatisfaction with the smile or facial features, because it is the time when women's awareness of their body increases. It is also easier for them to decide for themselves, because they earn money and have their own income which they can devote to taking care of their appearance. These patients also expect that results of the treatment of abnormal occlusion can be achieved as soon as possible. What is important – in women between 20 and 30 years hormonal balance stabilizes, which is unstable during adolescence. And since the hormones of the menstrual cycle start to play a constant, but unambiguous role in the body, filling the gap in science regarding their connection with the rate of tooth movement under the influence of orthodontic treatment seems to be indispensable.

Summary

Deepening knowledge about the influence of the menstrual cycle, and thus ovarian hormones on the flaccidity of ligaments in the tooth-alveolar joint and on the elasticity of the alveolar ridge may allow for more effective prophylaxis of periodontal diseases after orthodontic treatment in the future and for determining the best method to accelerate tooth movement under the influence of orthodontic forces.

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Piśmiennictwo do artykułów:

Korekta zgryzu głębokiego przy pomocy zmodyfikowanego aparatu Nance'a u dorosłego pacjenta z klasą II/2 i dehiscencją wyrostka zębodołowego

Correction of deep overbite by using a modified Nance appliance in an adult class II division 2 patient with dehiscence defect

Zhujun Li, Zhengxi Chen, Jian Sun, Li'an Yang, Zhenqi Chen

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Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego

Orthodontic tooth movement and changes in hormone levels during the menstrual cycle

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Wczesne leczenie ortodontyczne połowiczej mikrosomii twarzy

Early orthopaedic treatment of hemifacial microsomia

Diana Cassi, Marisabel Magnifico, Mauro Gandolfinini, Ilda Kasa, Giovanni Mauro, Alberto Di Blasio

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Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics?

Małgorzata Peruga; Beata Kawala; Michał Sarul; Jakub Kotowicz; Joanna Lis

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Article

Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics?

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Simple Summary: Animal experiments should be carried out in consultation with veterinarians, who, having clinical knowledge, will help doctors choose the appropriate animal model. Our review of the literature shows how the harmful and unethical duplication of research from other research centers can be. Familiarization with the experimental protocols on an animal model is important each time we want to later extrapolate the obtained results to the target species, i.e., human. This is due to the law on the implementation of the procedures on people. This article focuses on orthodontic teeth movement. While experiments with laboratory animals seem easy, there are many pitfalls. Our goal in this article is to collect data on the maintenance of laboratory animals as models and to critically analyze them based on our literature review.

Abstract: Animal testing was and remains the only method of introducing a certain treatment and medical procedure on humans. On the other hand, animals have their rights resulting from applicable legal acts, including Directive 2010/63/EU and, indirectly, the World Medical Association International Code of Medical Ethics (Helsinki Declaration, 1975, amended 2000). Thus, the question arises whether the credibility of the results of hormonal and orthodontic tests obtained so far and their usefulness for the human population is scientifically justified and worth sacrificing laboratory animals for. Especially that, according to statistical data, about 50% of laboratory animals are euthanized at the conclusion of the experiments. The aim of this article was to determine whether animal experiments are scientifically or morally justified in bringing significant evidence in studies that may validate the influence of changes in the concentration of female hormones secreted by the ovaries in various phases of the menstrual cycle in young patients on the duration of an increased tooth movement rate in orthodontic treatment. Papers reporting the results of the original research into female hormones, either natural or exogeneous ones, likely to alternate the orthodontic tooth movement rate were critically evaluated in terms of animal selection. Thorough analysis supported by veterinary knowledge proved that none of the publications enabled an extrapolation of the results to humans. The evaluation of the relation between the rate of tooth movement upon loading with orthodontic forces and hormones either secreted during the menstrual cycle of women or released from the contraceptives already present in the market, does not require sacrificing laboratory animals.

Keywords: veterinary ethics; qualitative and quantitative research designs; animal experimental model; steroid hormones

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1. The Use of Laboratory Animals in Orthodontics

Animal testing was and remains the only method of introducing a certain treatment and medical procedure on humans. The social acceptance of such experiments has been fervently debated since 13th century, when Saint Thomas Aquinas saw animals as useful machines, whilst Saint Francis of Assisi believed them to be humans' smaller brothers. Descartes continued the debate in the 16th century. However, the real rebellion aimed at anti-vivisection was pioneered by a woman, Fanny Matin, who in 1845 married Claude Bernard who was infamous for conducting experiments on stray dogs [1]. Noteworthy, at that time women had no voting rights, therefore Fanny Matin's opposition to vivisection reverberated across the scientific world and turned out to be the driving force behind the shift in the researchers' approach to respecting animals. Female sensitivity was also the catalyst for a mass protest in London. A conflict between Professor William Bayliss, a scientist who experimented on a terrier dog, thus discovering hormones, and whom the majority of the society considered to be a sadist, ended with a bronze monument of a dog being erected in London. The fate of a simple terrier had become the spur for adopting legislation protecting laboratory animals. However, it was not until the 21st century that the world of science changed forever: animals now have their 'protection' under existing legislation, including Directive 2010/63/EU [2], and it is primarily recognized in European Union countries. This directive was transposed into Polish legislation in 2015 [3], and states that animals must be provided with medical and veterinary care and conditions adequate to their health and until their natural death regardless of whether the experiment has ended. However, it must be emphasized that animals subjected to experiments very rarely fully recover, so their "natural" death issue is rather controversial [4]. Furthermore, animals react and metabolize substances differently in comparison to humans. For example, the lethal dose of potassium cyanide for rabbits and mice is, respectively, twice and seven times higher (obviously relative to their body mass) than for humans. In this term, many researchers, such as Ober [5] as well as Azkona [6], believe that in the case of interdisciplinary research work, cooperation between clinicians and scientists and qualified veterinarians is necessary.

Since experimental animals are present throughout all fields of science related to human healthcare, unsurprisingly, they are also involved in the development of dentistry, specifically in the field of orthodontics. The treatment of malocclusions in the case of young adult women, aged 20 to 30, is naturally linked to a menstrual cycle, which constitutes a sequence of recurring fluctuations of hormones that prepare the body for potential pregnancy: estrogens and especially progesterone. These hormones regulate osteoblast activity and the production of collagen, responsible—among other things—for a proper periodontal structure [7–12]. The natural cycle of sex hormones physiological fluctuations is disrupted by ovariectomy or hormonal contraception taken by a patient. Although modern oral contraceptives contain much lower doses of hormones when compared to medication used in the past, they still may damage periodontium, as they contribute shifting a balance between aerobe and anaerobe microorganisms towards the latter [13–15].

Any impairment in the alveolar bone structure immediately affects the rate of orthodontically induced tooth movement. It is therefore quite likely that if loading the teeth is planned in accordance with the menstrual cycle, one obtains the most efficient tooth movement due to the highest "plasticity" of periodontal tissues, which results in shortening the treatment time. Nevertheless, the World Medical Association International Code of Medical Ethics (Helsinki Declaration, 1975, amended 2000) requires that medical support, including orthodontic procedures, be carried out on at least two species, animals, before it can be used in humans [16]. Therefore, since the orthodontic experiment must burden laboratory animals so much, the credibility of the results of hormonal and orthodontic tests obtained so far and their usefulness for the human population should be critically assessed. Especially that, according to statistical data, about 50% of laboratory animals are euthanized at the conclusion of the experiments [17,18].

In this commentary, we aimed to determine whether animal experiments are scientifically or morally justified in bringing significant evidence to studies that may validate the influence of changes in the concentration of female hormones secreted by the ovaries in various phases of the menstrual cycle in young patients on the duration of an increased tooth movement rate in orthodontic treatment.

To this end, we searched PubMed, Elsevier ScienceDirect Journals, and EBSCOhost (Medline) electronic databases for laboratory research performed on animals, concerning orthodontic movement depending on the level of hormones during the menstrual cycle and while using hormonal contraceptives. We included review, clinical, comparative, intervention papers, and unusual cases, using the following keywords: estrogen, progesterone, hormonal contraception, menstrual cycle, heat, orthodontics, and orthodontic treatment. We disregarded the research performed on humans, as well as in vitro or in silico texts. We found 12 studies published between 1997 and 2022, which discussed the related subjects we target in this review.

2. Selected Studies

The impact of female hormones and hormonal contraception on orthodontic movement has been the subject of research in various centers, done on different species of animals. Most tests were done on Wistar rats, i.e., white rats used in pharmacological, toxicological, nutrition, and behavioral testing, but similar studies were performed on rabbits and cats. The canines, premolars, and incisors were moved predominantly. Open orthodontic springs and nickel and titanium wires were usually used for this purpose, with some studies using bone anchoring, i.e., mini implants. Some of the animals had their blood tested, others had their vaginal mucus tested. The tooth movement ranges were measured on gypsum dental casts poured on the examination day or inside the animals' mouths using a caliper. Most animals were euthanized after the research. Only healthy females took part in testing, with their own heat cycle or sterilized and exogenously administered with hormones [15,19–29].

The publications were divided into groups and specific publications were selected based on the scheme shown in Table 1.

Table 1. List of research methods and results obtained in papers analyzed as part of the review.

Authors	Animals and Their Division	Tooth and Type of Tooth Shift	Material Used	Method Used to Test the Hormone Level	Results
Olyaee et al. [15]	Wistar rats Age—3 months N = 48 m = 250 ± 25 g females	Central incisors tipped distally	SS spring with a diameter of 0.35 mm	Administration of ethinyl estradiol/norgestrel	Ethinyl estradiol/norgestrel (oral contraceptives) can decrease the amount of tooth movement
Guo, Zhao, Chen [19]	Wistar rats Age—not given N = 120 m = not given females	Not given	Not given	Estradiol level in serum and periodontium tissue using radioimmune and immune-cytochemical methods	Estrogen affects teeth movement
Zhao, Than, Guo, Chen [20]	Wistar rats Age—not given N = not given m = not given females	Not given	Not given	Estradiol level in serum and periodontium tissue using radioimmune and immune-cytochemical methods	Estrogen affects teeth movement
Guo, Zhao, Chen [21]	Wistar rats Age—3 months N = 80 m = not given females	Left upper incisor and left upper molar Tipped	Not given	Not given	Teeth movement dependent on cycle

Table 1. *Cont.*

Authors	Animals and Their Division	Tooth and Type of Tooth Shift	Material Used	Method Used to Test the Hormone Level	Results
Zhao, Than, Guo, Chen [22]	Wistar rats Age—not given N = not given m = not given females	Not given	Not given	Not given	Estrogen affects teeth movement
Guo, Zhao, Chen [23]	Rats, strain not given Age—not given Not given N = 200 m = not given females	Not given	Not given	Estradiol level in serum	Estrogen affects teeth movement
Haruyama et al. [24]	Wistar rats Age—10 weeks N = 85 m = 136 g females	right and left, first upper molar Tipped	NiTi spring with a diameter of 0.012 inch	Acc. to estrous cycle with vaginal smear	Estrus can increase tooth movement
Tan et al. [25]	Wistar rats Age—3 months N = 200 m = 300 g females	Left distal incisor and first left molar Tipped	NiTi spring with a diameter of 0.012 inch	Monitoring estrus cycle and vaginal smear	Estrus can increase tooth movement
Celebi [26]	Domestic cat Age—2–4 years N = 18 m = not given females	Jaw canine and mini implant Tipped	NiTi spring with a diameter of 0.2 inch	According to estrus cycle	Teeth movement speed was higher in sterilized specimens
Sirisoontorn [27]	Wistar rats Age—10 weeks N = 10 m = 170–190 g females	Left distal incisor and and first left molar Tipped	NiTi spring with a diameter of 0.012 inch	Monitoring estrus cycle and vaginal smear	Teeth movement speed was higher in sterilized specimens
Mackie et al. [28]	Sprague Dawley rats Age—6 weeks N = 55 m = 160 ± 20 g females	Right distal incisor and first right molar Tipped	NiTi spring with a diameter of 0.03 × 0.01 inch	Not given	Estrus can increase tooth movement
Poosti et al. [29]	Rabbit Age—8 weeks N = 24 m = 1850 g females	Central incisors tipped distally	SS spring with a diameter of 0.014 inch	Administration of progesterone	Progesterone affects tooth movement

Legend: N—number of animals used in testing; m—body mass of animal used in testing; SS—stainless steel; NiTi—nitinol.

3. Cross-Species Comparison with Humans

Factors crucial for hormonal and orthodontic experiments, differentiating women from female animals selected for testing, are shown in Table 2.

Table 2. Comparison of laboratory animals in terms of dentition, periodontium, reproductive cycle, body temperature.

Species	Size	Dental Formula	Teeth	Periodontium	Hormones	Body Temperature
Human (*Homo sapiens*)	Target species	$\frac{212}{212}$ $\frac{2123}{2123}$	Diphyodont Heterodont Bunodont	Thecodont Brachydont	Cycle 24–33 days Ovulation 24 h	36.6 °C
Laboratory rat (*Rattus*)	Acceptable size	X $\frac{1003}{1003}$	Monophyodont heterodont	Thecodont Monophyodont Incisors—hypsodont, elodont Molars—brachydont	Cycle 4–5 days Spontaneous ovulation Estrus 10–20 h	37.5–39 °C
Rabbit (*Oryctolagus cuniculus*)	Acceptable size	X $\frac{2033}{1032}$	Monophyodont Heterodont	Thecodont Hypsodont Elodont	Cycle 16 days Induced ovulation	38.5–40 °C
Domestic cat (*Felis catus*)	Acceptable size	$\frac{313}{312}$ $\frac{3131}{3121}$	Diphiodont Heterodont Secodont	Thecodont Brachydont	14–21 days	38–39 °C

Definition of terms (acc. to Kobryń, H.; Kobryńczuk, F.; Krysiak, K. *Anatomia Zwierząt Tom 1–3 (Animal Anatomy Vol. 1–3)*; PWN: Warsaw, Poland, 2011 [30]): X- does not occur; monophyodont—having one set of teeth; diphyodont—having two set of teeth; heterodont—with tooth shape differences between incisors, canines, premolars, and molars; thecodont—tooth embedded in a socket; brachydont—having short crowns with short growth time; hypsodont—having high crowns with long growth time; secodont—having sharp enameled teeth; bunodont—having rounded enameled teeth; elodont—teeth with an open top. An animal's dentition for either deciduous (first fraction) or permanent (second fraction) teeth expressed as a dental formula, written in the form of a fraction, as $\frac{I.C.P.M}{I.C.P.M}$ maxillary arch (above the line) and mandibular arch (below the line) I—incisors, C—canine, P—premolar, and M—molar, f.ex human 2123—2-I, 1-C, 2-C, 3-M.

4. Rats

Rats (Figure 1a,b) procreate quickly and their genes have also been well-mapped. Their transgenic strains, possible to be created nearly exclusively in small rodents, regardless of certain difficulties in maintaining their permanence, are still an important aspect favoring the selection of rats as experimental animals. This choice is also determined by the size of the animal, which facilitates the conduct of treatments and the preparation of histopathological materials. Rats are also cheap, which helps in testing their large groups. This is likely why rats were experimental animals in the majority of reviewed studies [15,19–25,27,28]. The evaluated studies theoretically demonstrated that the forced tooth movement rates are dependent on menstrual cycle or hormonal contraception. However, studies by Guo et al. [19,20,22] and Zhao et al. [21,23], performed at various intervals on various groups of rats, do not provide data for the measurements of the tooth movement and orthodontic biomechanics in relation to the heat cycle. The full-text articles are available only in Chinese, so we were able to review their abstracts, which merely summarized the research and did not fully report the results. We attempted to contact the researchers, but they did not reply to our emails. In turn, Mackie et al. [28] performed their tests on a strain other than Wistar, namely Sprague Dawley characterized by longer jaws, which naturally increases the distance between the incisors and the molars. Longer wires and springs are more easily deformed during chewing, when the so-called trampoline effect caused by the occlusal forces becomes evident [31]. Furthermore, the study used very young, 6-week-old specimens additionally subjected to stress that might drastically change their hormone levels; rats are less willing to reproduce when experiencing distress. As many as 4 specimens out of 55 died from stress, which undermines the entire test results, as the intensity of the metabolism is significantly increased during stress. In another study, also done on young rats, Olyaee et al. [15] used a spring between two incisors, which also challenges the reliability of the outcomes; due to the high probability of the not-fused palatal suture, the diastema quite likely resulted not from the tooth movement itself, but from separating the maxillary halves. Thus, it may be concluded that choosing a rat as an animal model for hormonal and orthodontic research is also unfounded. Although, similarly to humans, gaps between rat teeth (Figure 1c–e) are sufficiently wide to secure the natural drift of molars, and the teeth may be affected by caries; this is where the similarities end. Aside from the many evident differences (Table 2), the incisors in rats have enamel only on their front surfaces and they grow throughout the animals' lifetimes, which requires continuous sharpening of those teeth; in addition, the enamel is harder than metals such as iron, platinum, and copper. Continuous tooth eruption does not provide anchorage and sufficient control over the direction of force, which may lead to bias while interpreting the published data.

(d) (e)

Figure 1. Rat teeth in a skull: semi profile view (**a**), lateral view (**b**), premolars and molars view (**c**). Rat teeth: incisors, frontal view—enlarged overbite (**d**) and incisors, lateral view—enlarged overjet (**e**) (by Małgorzata Peruga).

As for the periodontal ligaments (PDL) of rats, they are built of connective tissue collagen fibers, which requires vitamin C (synthesized by rats in their kidneys or liver) to grow. Rats therefore do not have to obtain vitamin C exogenously, in contrast to humans, who do not produce L-gulonolactone oxidase (GULO), an enzyme contributing to vitamin C synthesis. It is worth noting here that although rats without GULO have been bred, they did not correctly reproduce the vitamin deficits seen in humans, which made the extrapolation of the obtained results impossible.

5. Rabbits

Rabbits, and specifically their thigh bones, are used in dentistry as a material for research into the osseointegration of implants. However, rabbit is an animal with a fragile anatomical structure, in particular its limbs, which often fracture under a load. Rabbits not only show little aggression toward humans but are also the smallest and the cheapest animals whose sperm can be harvested and used for artificial insemination. They produce tears and have large eyeballs, which facilitates the testing of chemical substances. However, apart from research into irritating substances, there is scant information available on other experimental studies. Poosti et al. [29] demonstrated that orthodontic movement changed after a female rabbit was provided with hormones from a human female that have a different chemical structure to their own hormones. The teeth of rabbits (Figure 2a–c), namely the incisors and the molars, can grow throughout their lifetimes. The incisors grow even two to three millimeters per week. Rabbits' teeth consist of clinical and anatomic crowns almost entirely covered by a layer of enamel absent at the top of the tooth, in the growth center. The PDL area is very limited (Figure 3a–c), which modifies the tooth behavior under loading with occlusal or orthodontic forces [32–34]. Mastication is also very different compared with humans. After reaching occlusal interdigitation, the rabbits' mandibular teeth rest on pegs (second part of the maxillary incisors) in a reversed overjet. To achieve normal occlusion, a rabbit must unilaterally and partially dislocate the mandibular condylar process from the fossa to close the arcade (Figure 4a,b).

(a) (b) (c)

Figure 2. Rabbit teeth: incisors frontal view—overbite (**a**) incisors lateral view—overjet (**b**) and premolars and molars view (**c**) (by Jakub Kotowicz).

(a) (b) (c)

Figure 3. Rodent incisor with open top and living pulp (**a**). Comparison with thecodont and brachydont dog tooth (**b**) and human tooth (**c**) (by Małgorzata Peruga).

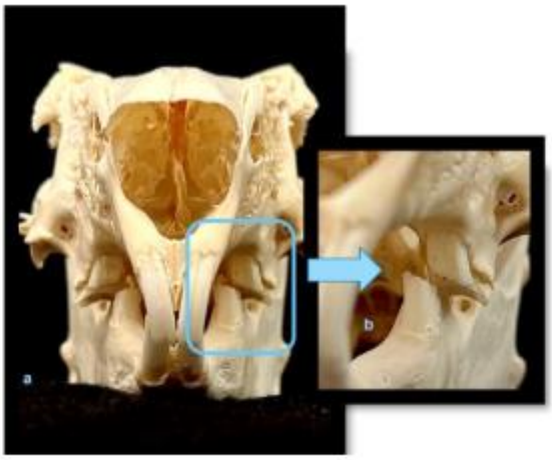

Figure 4. Anisognathism in rabbits: in 1:1 scale (**a**), enlarged (**b**) (by Małgorzata Peruga and Jakub Kotowicz).

Choosing rats and rabbits as test animals to assess the tooth movement during either a menstrual cycle or the administration of hormonal contraceptives is also controversial due to the fact that the estrus of these animals is too short [15,19–25,27–29,32–35] (Table 2) to notice visible changes in the three-stage process caused by orthodontic forces. Moreover, small animals do not match human biologically and do not live for long, not allowing for longitudinal studies.

6. Cats

Celebi et al. [26] used the domestic cat as a research model in hormonal testing. However, cats have no masticating surfaces (Figure 5a–c). The arrangement of their teeth in the dental arches and high degree of nodularity precludes using cats for orthodontic research, unless the bite is raised, which the authors did not mention describing their methodology (Table 2). Although cats are used as laboratory animals, due to the fact that their brain demonstrates the closest similarity to humans, these animals are primarily used in neurological, ophthalmological, and immune deficiency research, and not in hormonal and orthodontic studies.

Figure 5. Cat skull and teeth: semi profile view (**a**), lack of adhesion of the side teeth—scissor arrangement (**b**,**c**) (by Małgorzata Peruga).

In a nutshell, a good understanding of the anatomy and physiology of experimental animals will provide us with information that animals such as rats, rabbits, or cats were lacking validity as laboratory animals for orthodontic movement research. The analyzed articles (Table 1) found numerous errors in the research assumptions, due to the fact that the authors did not take into account the important aspects that were pointed out, such as the different anatomical structure of teeth and periodontal and completely different occlusions.

7. Hormone Cycle

Most studies into the relation between the rate of the tooth movement and the action of hormones secreted during the menstrual cycle were done on animals, who were administered human progesterone, estrogens, and relaxin [36–41]. As far as progesterone is concerned, experimental research on rats has demonstrated that the hormone modified the orthodontic movement of their teeth by affecting the periodontium and elasticity of the cortical plate of the alveolar process. On the other hand, the long-term administration of progesterone to rabbits resulted in a reduced rate of the tooth movement; the authors concluded that it was due to the fact that osteoclasts are observed primarily 2 days after an orthodontic force is applied [31]. Administering relaxin to rats resulted in an increase in the rate of orthodontic tooth movement when compared to control groups, as well as the stretching of periodontium made of soft tissue [42–45]. Unfortunately, as the normal hormonal cycle of animals was disrupted in every reviewed study, it cannot be stated with certainty whether the changes in the rate of tooth movements were caused only by the excessive amount of artificially introduced hormones or a disruption in the natural hormonal balance, particularly given the short observation period.

8. Orthodontic Materials

Most of the reviewed studies used materials made from nickel and titanium (NiTi) alloy, which has been popular in orthodontic treatment since the 1970s. Its elasticity modulus approximately equals 20% of the modulus of the stainless steel, which secures a very wide scope of working elasticity. The complex metallurgical nature of nickel and titanium materials and its relation to clinical application have been the subject of many scientific studies. It has been demonstrated that the NiTi alloy has two phases. The first phase, austenitic, has an ordered structure, whereas the second phase, martensitic, is a highly strained body-centered tetragonal form. Shape memory is linked to the reversible transformation of martensite into austenite, which occurs as a result of a crystallographic process. The microstructure of alloys in the temperature found in the human oral cavity (36.1–37 °C) is not fully austenitic. The temperature of the complete transformation to austenite is 40 °C, which is evidently higher than the temperature in the oral cavity. That is why the alloy will behave differently in patients breathing through their mouth (27 °C) or consuming hot food (40 °C). The issue of the natural bodily temperature of animals [46] cannot therefore be ignored, as it changes the behavior of the nickel and titanium spring.

9. Conclusions

Many experimental tests have so far been done on various species of animals to obtain a better understanding of their biological reactions to orthodontic forces. Unfortunately, one of the main problems related to animal experiments is the fact that their results cannot be extrapolated to humans. The two- or even four-year lifespans of rats and rabbits, respectively, together with short estrus, enable us only to observe the immediate effects of the tooth loading, which are impossible to extrapolate on humans due to severe dissimilarities of the tooth anatomy, their PDL, as well as female hormone secretion cycles. Additionally, the lack of long-term results, which are the most reliable scientifically, is a serious limitation of the so-far designed experimental studies. The orthodontic treatment of humans with fixed appliances has been ethically accepted since at least the beginning of the previous century. Thus, evaluating the relationship between the rate of tooth movement upon loading with orthodontic forces, and hormones either secreted during the menstrual cycle of women or released from the contraceptives already present in the market, does not require experimental testing. It is enough to interview the patient and to determine the adequate timing of a force application, with subsequent measuring of the rate of the tooth movement during scheduled appointments. Perhaps a "reductio ad absurdum" argument is irresponsible; however, orthodontic treatment is carried out successfully and, above all, does not involve any risk, because the general principles of mechanics and biomechanics are known. Our results should encourage researchers to analyze the methods and selection of animals for research in more detail. There is no moral justification for performing orthodontic examinations on rats, rabbits, or cats, which we have proved.

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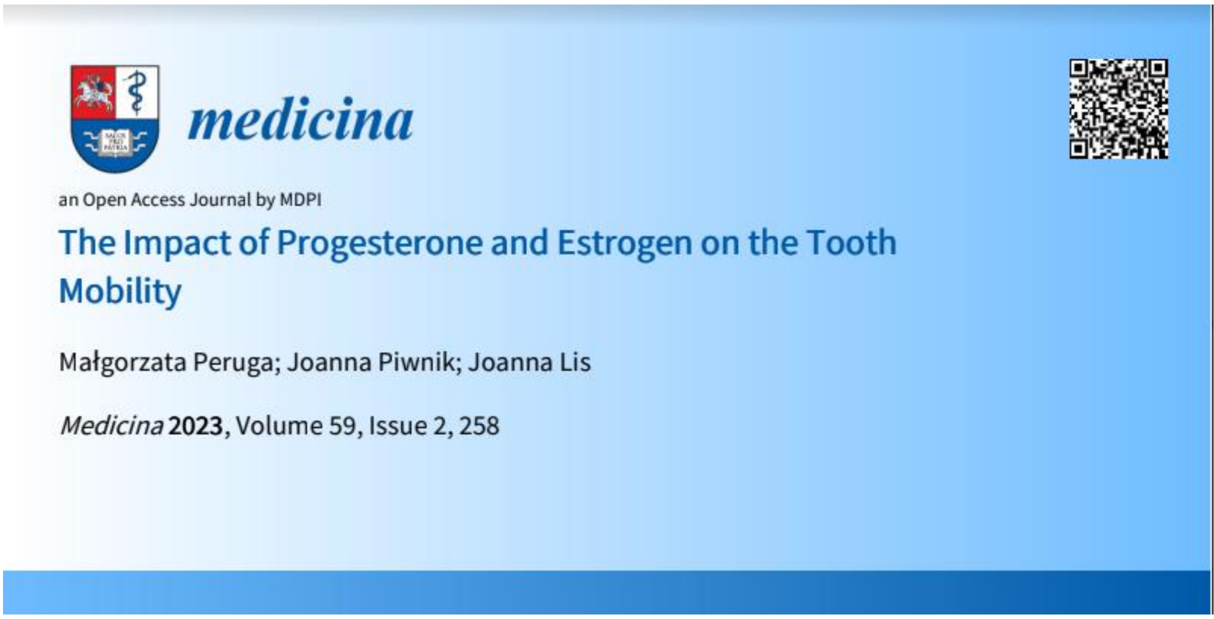

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Article

The Impact of Progesterone and Estrogen on the Tooth Mobility

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Abstract: *Background and Objectives*: Progesterone and estrogen modify the bone metabolism directly related to the periodontium, this study aimed at answering the question whether fluctuations in the levels of these hormones or the use of their synthetic equivalents in modern contraceptives have a significant impact on the natural tooth mobility (TM) in its alveolus. *Materials and Methods*: Sixty healthy women who had never been pregnant and when interviewed reported either (1) having regular menstruations every 28–30 days or (2) taking oral two-phase two-ingredient hormonal contraceptives formed, respectively, groups M and S in the study. TM evaluated as the Periotest value (PTV) was checked in the menstruation, ovulation, and luteal phases of the menstrual cycle (group M) and on the days corresponding to the moment of the menstrual cycle in group S. *Results*: Although the PTV-s were within the limits of norm, the canines and the molars were always more stable than the other teeth. In group M, the TM was statistically comparable ($p > 0.05$) in the menstrual and ovulation phases, thus significantly increased ($p < 0.001$) in the luteal phase. The TM remained constant ($p = 0.758$) in all studies in group S. The results demonstrated that the canines and the molars in the luteal phase were significantly more mobile in group M than in group S ($p < 0.001$), although increased mobility of the teeth in group M affected the canines and the first molars to a significantly lesser degree than the other teeth. *Conclusions*: However, since women between 20 and 30 years old constitute the majority of ortho-dontic patients, possible determination of the optimum moment of force application in relation to the sex hormones cycle, namely, to its luteal phase, is clinically very promising.

Keywords: progesterone; estrogen; hormonal contraceptives; periodontal ligaments; bone metabolism; tooth mobility

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1. Introduction

The female menstrual cycle is a sequence of recurrent hormonal fluctuations, primarily of estrogen and progesterone. Levels of these hormones differ in various periods of women's lives: adolescence, menstruation, pregnancy, menopause, or when taking hormonal contraceptives [1,2].

Estradiol is an estrogen produced by female gonads, placenta, and some peripheral tissues (mainly adipocytes). It plays a key role in the development of secondary sex characteristics, and also contributes to the development of the limb and axial skeleton [3–5]. The latter effect is of key importance for orthodontists and periodontologists, as the periodontium is made of—among others—the cortical plate of the alveolus with an adjoining scaffolding of cancellous bone trabeculae. Estrogen and progesterone receptors are also located in other periodontal components, namely, the gingiva and the periodontal ligaments [6,7], so it has already been proven that estrogen exerts a range of effects on tissues in the periodontium [8–10]. By regulating the production of epithelial glycogen, it reduces the keratinization of the gingiva, ultimately decreasing the role of the epithelial barrier. It reduces the reaction of T-lymphocytes, thus leading to an increased occurrence of gingival inflammations, without favoring dental plaque formation. Estrogen also stimulates the proliferation of fibroblasts and the synthesis and maturation of tissues composing the gingiva. It reduces the production of leucocytes in bone marrow, impeding the release of pro-inflammatory cytokines by human marrow cells [11,12].

Progesterone is released by the corpus luteum, placenta, and adrenal cortex. The literature on orthopedics presents an extensive body of information on its impact on bone metabolism and the effects on ligaments. It expands vascular beds, increasing their permeability. It stimulates the production of prostaglandins and contributes to increased levels of multinuclear leucocytes, in contrast to estrogen [2]. Progesterone impedes the synthesis of collagen present in the periodontal ligaments. As a result, their potential to repair reduces, as does the number of their fibers. An increase in the level of progesterone accelerates the metabolic decomposition of folic acid required for growth, development, and proliferation of the cells. Progesterone levels are the highest during the luteal phase of the menstrual cycle, namely, 7 days after ovulation, whereas estrogen levels are the highest during ovulation [1,2,10].

The natural cyclicality of fluctuations of the discussed hormones is disrupted by using hormonal contraceptives, the effects of which include stopping ovulation. Women who have not given birth are usually prescribed two-ingredient two-phase pills, which contain ethinylestradiol and synthetic equivalents of progesterone–gestagen. These pills change the level of estrogen and gestagen throughout the entire menstrual cycle, in contrast to single-phase pills [12–16]. Current contraceptives contain much lower doses of hormones than pills used in the past. Nevertheless, it has been proven that modern contraceptives may still significantly modify the immune response, resulting in a risk of damage to the periodontium due to an increased number of anaerobic bacteria in comparison to aerobic bacteria and the increased prevalence of tooth decay [16–21].

Given the fact that progesterone and estrogen modify the bone metabolism directly related to the periodontium, a question arises whether fluctuations in the levels of these hormones or the use of synthetic equivalents in modern contraceptives have a significant impact on the natural mobility of the teeth in their alveoli.

Objective of the Study

The objective of the study was to assess the profile of the tooth's natural mobility in the alveolar processes during the menstrual cycle and while taking hormonal contraceptives.

2. Materials and Methods

2.1. Materials

Participants in the study were chosen among women in good general health, with a normal body mass index (18.5–24.9), who reported for an orthodontic consultation to the individual medical practice, had never been pregnant, and when interviewed reported either (1) having regular menstruations every 28–30 days or (2) taking oral two-phase two-ingredient hormonal contraceptives for at least four months, which was the factor deciding which group a given participant was assigned to. With regard to oral health, the inclusion criterion was the lack of both the chronic inflammations in the oral cavity and the active caries lesions. A total of 113 women were initially enrolled in the study; the process of further selection based on the application of exclusion criteria is shown on the flowchart (Figure 1).

All women that required conservative, periodontal, or surgical treatment, as determined during an initial examination, received appropriate referrals to dental specialists. Women with irregular menstruations were referred to a gynecologist.

Ultimately, 60 women between 20 to 30 years old qualified for the prospective study. Written informed consent for testing was obtained from all participants; the tests took place between January and April 2019.

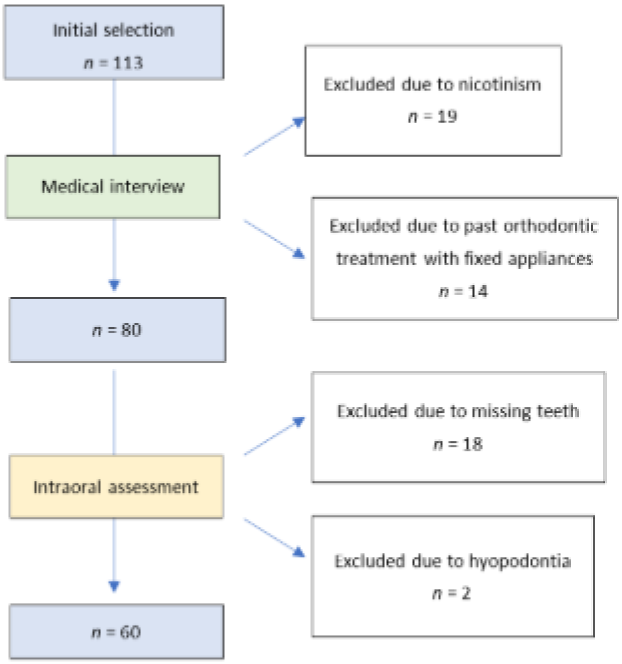

Figure 1. Flowchart of the study material selection.

2.2. Methods

Chosen women were divided into two groups that underwent a series of three examinations (Table 1). Each participant was instructed to report for testing on strictly specified days and at a specific, constant time.

The examination was designed to enable achieving the goal of our study. For this purpose, a single sample of venous blood was always taken at 7.00 am, each time from the cubital fossa to assess the axis of the hypothalamus–pituitary gland–ovary and to determine the blood levels of progesterone and estrogen subsequently evaluated by a gynecologist. The tooth mobility was assessed objectively using a Periotest electrical device that measures the deviation and reduction in speed of a small headpiece (that comes out from inside the machine) while it hits a tooth in its alveolus. Contact time is converted into numerical values of the Periotest, referred to as PTV (Periotest value). The range of the Periotest values was −8 to +50. The higher the PTV, the higher the mobility of the tested object [22–24]. Three measurements were taken at each tooth, and the average result was recorded.

Table 1. Composition of the study material and timing of the examination.

	Examination		
	I	II	III
Women who menstruate, group M $n = 30$	Third day of the cycle Menstruation phase	Ovulation day Ovulation phase	7 days after ovulation Luteal phase
Women taking contraceptives, group S $n = 30$	1st day *	42nd day *	77th day *

* Day corresponding to the moment of the menstrual cycle in group M.

2.3. Statistical Analysis

The StatSoft Statistica 13.3 software package was used to perform a statistical analysis of the intra- and intergroup comparisons of the clinical parameters. The significance level was set to $\alpha = 0.05$. The Shapiro–Wilk test was used to examine the normality of the data distribution. As the data distribution was not normal, the results were presented as a median (interquartile range, IQR). The Kruskal–Wallis non-parametric test was used to compare the tooth mobilities within groups M and S and the Mann–Whitney U test was used to compare the mobility of each tooth between groups M and S. Median ranges of all group pairs were compared in order to perform a post-hoc analysis. Results of the post-hoc analysis were evaluated using the Mann–Whitney U test. The mobility of the teeth in group M was compared using Friedman's ANOVA non-parametric, and the Wilcoxon test was twice used for post-hoc analysis. Mobility of the teeth in group S was compared using the Mann–Whitney U test, reducing the level of significance in multiple comparisons using the Bonferroni correction.

3. Results

Despite all of the PTV results being within the normal range, the results of the examinations from I to III demonstrated that the tooth mobility varied, namely, the median PTV values in both groups differed statistically (Table 2). Moreover, the canines and the molars were always significantly more stable than the other teeth (Table 3). Significantly lower mobility of the canines and the molars in comparison with the other teeth was independent of both the day of the menstrual cycle and the duration of using contraceptives.

In women who menstruated (group M), the tooth mobility was statistically comparable ($p > 0.05$) in examinations I and II (i.e., during the menstrual phase and during ovulation), however, increased significantly ($p < 0.001$) in examination III (i.e., in the luteal phase of the menstrual cycle). The tooth mobility remained constant ($p = 0.758$) in all examinations in group S, irrespective of the duration of medication (Table 4). This mobility was significantly higher in women from group M than in women from group S. The highest difference occurred in examination III, and therefore it underwent additional comparative analysis. For its purpose, homonymous teeth in both quadrants were treated as one, which resulted in a lower number of multiple comparisons (Table 5). The results demonstrate that the canines and the molars in examination III were significantly more mobile in group M than in group S ($p < 0.001$), although increased mobility of the teeth in group M affected the canines and the first molars to a significantly lesser degree than the other teeth.

Table 2. Statistical analysis of the intra-group differences of PTV (obtained for the individual teeth).

	Group	Tooth	16	15	14	13	12	11	21	22	23	24	25	26	*p*
Examination I	M	Median (IQR)	0 (−0.3,0)	1 (0.4,2)	1 (0.3,2.8)	−0.1 (−0.2,0.1)	2.1 (1.5,3)	2.1 (1.2,2.8)	2 (1.2,2.7)	2 (1.4,3)	−0.1 (−0.2,0.1)	1 (0.3,2.8)	1 (0.4,2)	0.1 (0,0.5)	<0.001
	S		0 (0.4,0.4)	1 (0.3,2.1)	1 (0.5,2)	−0.1 (−0.5,0.1)	2 (1.5,3.2)	1.8 (1.2,3.2)	1.9 (1.1,3.1)	2 (1.3,3)	−0.1 (−0.4,0)	1 (0.5,2)	1 (0.6,2.1)	0.2 (0,0.9)	<0.001
		p	0.40	0.89	0.58	0.60	0.97	0.86	0.72	0.84	0.14	0.58	0.21	0.33	
Examination II	M	Median (IQR)	0.2 (0,0.9)	1 (0.6,2.1)	1 (0.3,2.8)	−0.1 (−0.2,0.2)	2.1 (1.6,3)	2.1 (1.2,2.8)	2.1 (1.2,2.7)	2 (1.4,3)	−0.1 (−0.2,0.1)	1 (0.3,2.8)	1 (0.4,2)	0.4 (0.1,0.8)	<0.001
	S		−0.1 (−0.4,0.4)	1.1 (0.6,2.5)	0.9 (0.6,2.3)	−0.1 (−0.4,0.2)	2 (1.7,3.2)	2.1 (1.1,3.1)	1.7 (1.1,3)	1.9 (1.2,3)	−0.2 (−0.5,0)	1 (0.6,2.1)	1.3 (0.5,2.2)	0.2 (−0.4,0.8)	<0.001
		p	0.026	0.98	0.75	0.36	0.83	0.75	0.59	0.73	0.12	0.54	0.55	0.20	
Examination III	M	Median (IQR)	1.1 (0.5,1.9)	1.2 (0.6,2.3)	1.1 (0.4,3)	0.1 (0,0.4)	2.1 (1.6,3.1)	2.2 (1.3,3)	2.2 (1.3,2.8)	2.2 (1.5,3.1)	0 (0,0.2)	1 (0.4,3)	1.1 (0.6,2.1)	1.1 (0.8,1.9)	<0.001
	S		0.1 (−0.5,0.5)	1.1 (0.3,2.1)	1.3 (0.4,2.3)	−0.2 (−0.6,0.2)	2.2 (1.2,3.4)	2 (1.2,3.4)	1.9 (1.4,3.1)	2.2 (1.2,2.9)	−0.3 (−0.6,0.1)	0.9 (0.3,2.4)	1.3 (0.8,2.3)	0.3 (−0.2,1)	<0.001
		p	<0.001	0.35	0.78	0.019	0.78	0.89	0.62	0.61	0.006	0.77	0.27	<0.001	

Table 3. Statistical analysis of the intra-group PTV differences between the teeth demonstrating higher and lower stability.

	Examination I				Examination II				Examination III			
Group	**M**	**S**	**M**	**S**	**M**	**S**	**M**	**S**	**M**	**S**	**M**	**S**
Stability	**Median (IQR)**		**Mean**		**Median (IQR)**		**Mean**		**Median (IQR)**		**Mean**	
Higher +C+, +M1+	0 (−0.2,0.2)	0 (−0.3,0.2)	−0.05	−0.07	0.1 (−0.1,0.5)	0 (−0.2,0.2)	0.15	−0.07	0.5 (0,1.15)	0 (−0.4,0.4)	0.74	−0.07
Lower +I1+, +I2+, +P1+, +P2+	1.45 (0.9,2.6)	1.5 (0.9,2.6)	1.80	1.83	1.5 (1,2.6)	−0.1 (−0.4,0.3)	1.85	1.83	1.55 (1.05,2.75)	1.6 (0.9,2.6)	1.92	1.84
p	<0.001	<0.001			<0.001	<0.001			<0.001	<0.001		

Legend: +M1+—the first molars; +P2+—the second premolars; +P1+—the first premolars; +C+—the canines; +I2+—the lateral incisors; +I1+—the central incisors.

Table 4. Statistical analysis of both the intra- and the intergroup median PTV differences between all examinations.

	Group M	Group S	Total	*p*
Examination I	1 (0.15,2.1)	1 (0.2,2)	1 (0.2,2.05)	0.667
Examination II	1 (0.2,2.1)	0.9 (0.2,2.1)	1 (0.2,2.1)	0.386
Examination III	1.2 (0.5,2.3)	0.9 (0.1,2.2)	1.1 (0.3,2.2)	<0.001
p	<0.001	0.758		

Table 5. Statistical analysis of the intergroup PTV differences in examination III.

Tooth	Group M		Group S		
	Median (IQR)	Mean	Median (IQR)	Mean	*p*
+I1+	2.2 (1.3,2.8)	2.35	1.95 (1.4,3.2)	2.21	0.65
+I2+	2.15 (1.5,3.1)	2.48	2.2 (1.2,3)	2.32	0.59
+C+	0 (0,0.2)	0.1	−0.2 (−0.6,0.2)	−0.24	<0.001
+P1+	1.05 (0.4,3)	1.42	1.05 (0.4,2.4)	1.47	0.67
+P2+	1.1 (0.6,2.2)	1.43	1.2 (0.7,2.1)	1.40	0.98
+M1+	1.1 (0.6,1.9)	1.34	0.1 (−0,3,0.6)	0.08	<0.001

Legend: +M1+—the first molars; +P2+—the second premolars; +P1+—the first premolars; +C+—the canines; +I2+—the lateral incisors; +I1+—the central incisors.

4. Discussion

During the menstrual cycle in healthy women in their procreative period, the level of progesterone rises until the seventh day after the egg cell is released from the ovary, and then—if fertilization occurs—continues to occur in later stages of the pregnancy [1]. Without fertilization, the levels of progesterone in the patient's blood drop, resulting in menstruation in further cascade reaction. In healthy women, progesterone levels should range between 0.057 and 0.893 ng/mL during the follicular case, between 0.121 and 12.0 ng/mL during the ovulation phase, and between 1.83 and 23.9 ng/mL during the luteal phase. In post-menopausal women, these levels should range from 0.05 to 0.126 ng/mL [1,2]. To ensure that the values have a point of reference in any study, the study must include women from a homogenous group, which was the case in our study. Participants in our study were women of similar ages, from whom we sampled blood at a constant set time, within a short period of time (January–April). In this way, we were able to rule out the impact of factors such as age, time of day, and season on the result of the test. By referring to numerical data [1], which indicated the level of progesterone in the luteal phase increases by nearly four times in comparison to the follicular phase, the PTVs we obtained in study III in group M enabled us to identify this hormone as the driving force behind the increased average mobility of teeth.

Choosing Periotest as a measurement instrument was also fully justified. Periotest is widely accepted and used to measure mobility in vivo and in vitro in periodontology, implantology, orthodontics, and traumatology. The advantages of the Periotest include its ease of use, ability to make measurements in the horizontal and in the vertical dimensions, and primarily the repeatability of results [22,25]. Thus, our studies can be reproduced at any scientific center or even a medical practice.

As the PTVs measured in our tests ranged between −8 and +9 [26], which is considered proof of stability of a tooth, we were able to demonstrate that changes in the female menstrual cycle caused by contraceptives do not have a destructive effect on young and healthy periodontium.

However, this does not mean that there is no link between the movement of teeth and contraceptives. On the contrary: the long-term use of hormonal pills has a stabilizing effect on the anchoring of the teeth in the alveolus, as the tooth mobility among women who took contraceptives (group S) was higher than in menstruating women (group M) only in examination I. In further examinations, tooth mobility was greater in group M than in group S, although a statistically significant inter-group difference was observed only in examination III.

The use of hormonal therapies is an important issue for both orthopedists and dentists, as it may result in disruptions to the physiological development of bone and its density [1]. Unfortunately, there too few studies have been conducted on adolescent women, and those that involved young and mature women not only did not formulate clear conclusions on the effects of taking hormonal contraceptives, but also had divergent results [27,28], and as such offer little value as evidence. However, the fact that estrogen promotes the termination of bone growth including the mandible has been demonstrated beyond doubt [29–33], and therefore the effects of this hormone may affect the tooth mobility.

Since the metabolism of the alveolar ridge cannot be considered the cause for the changes in PTV among women who menstruate and women who take hormonal contraceptives, we needed to focus on the second component of the periodontium, namely, the periodontal ligaments, particularly as the literature indicates that hormonal contraception leads to an increased risk of breaking the attachments of ligaments in the knee joint [34–37]. In this aspect, our results are hugely significant. Without animal testing, we were able to demonstrate that the impact of progesterone and estrogen on the periodontium was different to that on the rest of the human system: we did not observe any reduction in the function of periodontal fibers in the representative, homogenous group S.

Hyperplasia of the gingiva—another part of the periodontium—is a documented phenomenon in healthy women who use hormonal contraceptives in the long-term [38–40]. Unfortunately, researchers have been unable to determine the limit dose of hormones that affects the above-described changes [41–43]. However, as sex hormones reduce the immune response of the gingiva to the dental plaque, hormonal contraception, in particular estrogen-based, may intensify the action of localized irritating factors [44,45], especially given that estrogen is responsible for keratosis of the gingiva and proliferative changes in its epithelium and increased fibroblast activity [1,2,10]. On the other hand, by increasing the permeability of microvessels, progesterone causes increased irritability and swelling of the gums and facilitates the resorption of bones and reduces collagen production, in this way promoting the catabolism of tissues and hampering their repair, and as such, may deepen gingival pockets, particularly with improper hygiene [1,2,10,41–43]. All of these processes contribute to the destabilization of the anchoring of teeth in the alveoli, but the obtained PTVs did not confirm the occurrence of this negative phenomenon.

The bacterial biofilm is another important area that was studied in terms of the effects of progesterone and estrogen on the movement of teeth. Bacterial biofilm is defined as a highly specialized, single- or multi-species form of microorganism life, permanently located on its substrate and surrounded by a layer of extracellular polysaccharides that create mucus [45]. Pioneers inhabiting the biofilm include strep bacteria: *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguis*. Other microorganisms include *Actinomyces* and Gram-negative bacteria (e.g., *Haemophilus*) [46]. They reduce the resting pH of the dental plaque [47–49], which reaches its lower values (pH = 4) near the maxillary incisors. This is associated with the free flow of saliva that contributes to the long-term retention of acids in the dental plaque as well as with the weight of saliva and distance between the incisors and the openings of salivary ducts [50]. Low pH leads to fast fluoride loss and reduces its cariostatic action, the limit point of which is pH = 4.5 [49,51]. *Streptococcus mutans* and *Lactobacillus* may reduce the pH of the dental plaque to <4.5, which is of huge importance, as Ali et al. [16] noted that the number of bacteria in women taking oral contraceptives was increased. The researchers stressed that the long-term use of hormonal contraceptives had a destructive effect on the delicate structures of the periodontium. Another significant fact related to these structures is that low pH contributes to an increase in the number of microorganisms from the *Candida* genus (i.e., *Porphyromonas gingivalis*, *Porphyromonas intermedia*, and *Actinobacillus actinomycetemcomitas*) in the gingival pockets [16]. As contraceptives are conducive to the proliferation of microorganisms, which cause the acidification of the oral cavity, which in turn poses a threat to the periodontium, increased mobility of teeth in the frontal section should be expected [16]. This was confirmed by the results of our studies, in which women who took contraceptive pills had less stable incisors than in women with a physiological menstrual cycle, in every phase.

With regard to the modern scope of our study, nowadays, oral contraceptives are safe and effective. The previous generation of medication contained much higher doses of synthetic hormones than those currently used and was based on a single ingredient, causing much more disruption [52]. Hormone doses had to be reduced due to their harmful effects on the cardiovascular system in large doses [1,2,10]. Unfortunately, despite the widespread and long-term use of oral contraception around the world, there is still no clear data on its impact on the condition of the bones of teenagers and young adult women available. Studied parts of the body (spinal bones, femoral necks, alveolar process), dates of studies (the 1980s and the early 21st century), their durations (from 1 year to 5 years), length of use of contraceptives and their types, and populations of studied patients (ethnic origin, age of 14 to 30, body mass, height) significantly varied. Therefore, interpretation of the results of all studies is extremely difficult. Studies undertaken on young women on short-term hormonal therapy in low doses did not show any changes in bone build and disorders in the periodontium. It has to be noted that selecting patients is quite difficult, as long-term studies of young adults taking hormonal contraceptives are often limited due to discontinuation or change of medication, and result in their hormonal composition. Nevertheless, these studies continue to create opinions among dentists, who are convinced that oral contraceptives increase the risk of gum and periodontal inflammation. It is worth noting that in order to determine whether modern oral contraceptives have any effect on the periodontium, much fewer studies have been conducted using modern medication than older generation medicines. Despite the incontrovertible significance of the results of our study on the impact of modern contraceptives on the periodontium during their use, we cannot lose sight of the observations of the long-term effects that are required from the scientific perspective and evidence-based medicine.

5. Conclusions

Given the fact that progesterone and estrogen modify the bone metabolism directly related to the periodontium, this study aimed at answering the question of whether fluctuations in the levels of these hormones or the use of their synthetic equivalents in modern contraceptives have a significant impact on the natural tooth mobility (TM) in its alveolus. Long-term use of hormonal pills has a stabilizing effect on the anchoring of teeth in the alveolus, as the tooth mobility among women who took contraceptives (group S) was higher than in menstruating women (group M) only in examination I. In further examinations, tooth mobility was greater in group M than in group S, although a statistically significant inter-group difference was observed only in examination III. Although the PTVs were within the limits of norm, the canines and the molars were always more stable than the other teeth. Although the exam involved a large group of women, the results of our research into the impact of hormonal contraception on PTVs are still merely preliminary findings.

However, since women between 20 and 30 years old constitute the majority of orthodontic patients, possible determination of the optimum moment of force application in relation to the sex hormones cycle, namely, to its luteal phase, is clinically very promising. Certainly, determining whether long-term intake of contraception may change the bone and periodontal ligament structures and whether such changes are reversible after the patient ceases to take medication, and if so, how quickly they reverse after medication is stopped, requires long-term studies.

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Original Article

Correlation of sex hormone levels with orthodontic tooth movement in the maxilla: a prospective cohort study

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Summary

Background: Sex hormones secreted during the menstrual cycle and the application of orthodontic forces to teeth can affect the metabolism of periodontal ligaments. This study aimed to determine whether there are any differences in orthodontic tooth displacement during the menstrual cycle and when using hormonal contraceptives and whether the amount of female sex hormones influences the efficiency of tooth displacement.

Methods: A total of 120 women aged between 20 and 30 years with Angle Class II requiring transpalatal arch (TPA) to derotate teeth 16 and 26 were included in this study. The participants were divided into two groups: group A, which included women with regular menstruation, and control group B, which included women taking monophasic combined oral contraceptives. Group A was divided into subgroups according to the moment of TPA activation: menstruation (A1), ovulation phase (A2), and luteal phase (A3) (examination I). On intraoral scans, measurement points were marked on the proximal mesial cusps of teeth 16 and 26, and the intermolar distance (M^1) was determined. The change in the position of the measurement points 6 weeks after activation (examination II) made it possible to determine the derotating extent of teeth 16 (O16) and 26 (O26) and the widening of the intermolar distance (M^2–M^1). In examinations I and II, tooth mobility in the alveoli was assessed using Periotest based on the periotest values (PTV) PTV^1 and PTV^2, respectively.

Results: A significant difference in all parameters was observed among groups A1, A2, and A3 ($P < 0.001$). Group A3 showed the highest values of parameters O16, O26, and M^2–M^1, and group A2 showed the lowest values, which did not differ from the control group ($P = 0.64$). PTV^2 and PTV^1 were the highest in group A3 and the lowest in groups A1 and B. Intergroup differences were statistically significant ($P < 0.001$).

Conclusions: With the quantification of changes in tooth mobility in the alveoli during the menstrual cycle in women undergoing orthodontic treatment, it was possible to determine that female sex hormones affect the effectiveness of orthodontic treatment, and the optimal moment for TPA activation is the luteal phase of the menstrual cycle.

Keywords: progesterone; estrogen; contraception; periodontal ligaments; bone metabolism; orthodontic tooth movement

Introduction

Sex hormones, namely, progesterone and estrogen, secreted during the menstrual cycle, directly affecting the amount of insulin-like growth factor-I (a mediator of collagen production) and carboxy-terminal telopeptide type I collagen (a marker of type I collagen degradation), cause cartilage growth, strengthen collagen and proteoglycan synthesis, and promote calcium, magnesium, and potassium homeostasis [1]. In addition, they affect the metabolism of periodontal ligaments (PDL), which causes the mobility of the tooth in the alveoli to change and reach its greatest value during the menstrual phase [2]. Acute fluctuations in hormone concentrations across a woman's menstrual cycle, specifically higher estradiol levels, can inhibit collagen synthesis and reduce ligament strength [1].

Furthermore, orthodontic forces applied to the tooth can cause changes in the functioning of the PDL. When exposed to mechanical force, a coordinated signaling cascade is activated, involving various cell types, including PDL fibroblasts, mesenchymal stem cells, inflammatory cells, osteoblasts, osteocytes, and osteoclasts [3]. This induces bone remodeling and tooth displacement, which consists of three stages, namely, initial tipping, delay phase, and progressive displacement. In the initial tipping phase, the PDL is compressed adjacent to the alveolar bone on the side where the force is directed, and on the opposite side, the PDL lengthens and tightens. This phase is followed by a delay phase or cell mobilization, which allows the PDL and bone to remodel with osteoclasts and osteoblasts. The length of this phase depends partly on the applied force. An excessive amount of force causes the root to move too close to the alveolar wall. The blood vessels are then compressed, and the movement of the tooth slows down. This stage can last from several days to several weeks. The final phase is characterized by actual bone remodeling with apposition in tension areas and resorption in compression areas. This process results in tooth movement [4].

Considering these facts, a question arises: Does the secretion of progesterone and estrogen, which affect the PDL reaction, contribute to changing the effectiveness of malocclusion treatment? Experimental, epidemiological, and clinical data indicate that progesterone is involved in bone metabolism. Progesterone acts directly on bone by engaging an osteoblast receptor or indirectly by competing for a glucocorticoid osteoblast receptor, promotes bone formation, and increases bone turnover. Estrogen increases the number of vitamin D3 receptors. Progesterone plays a role in the coupling of bone resorption and formation by increasing the binding of progesterone to the osteoblast receptor, which is stimulated by estrogen. A relationship has been reported between osteoporosis and bone fragility and a decline in estrogen levels during the menstrual cycle. In addition, compelling evidence has shown that bone-destroying cytokines, such as IL-1, IL-6, and TNF-α, are released and increase rapidly as estradiol levels decline [5]. From this perspective, a normal ovulatory cycle is a natural coherence cycle that activates the bones [6]. Mechanically induced tooth movement is associated with the risk of various complications [7, 8] and is an extremely complex process. Therefore, it is important to understand the factors that affect the outcomes of orthodontic treatment of malocclusion in young and adult women who are interested in improving their appearance.

This study aimed to determine whether the pattern of orthodontic tooth displacement changes when using hormonal contraceptives and during menstruation and whether the amount of female sex hormones in the body affects tooth displacement efficiency. We hypothesize that there is a 0.05-unit difference in tooth mobility measured by the O parameter, which represents the extent of rotation of teeth 16 (O16) and 26 (O26) and is considered the most important parameter in this study, at different times in the menstrual cycle.

Materials and methods

Study design

This prospective cohort study was conducted at the Orthodontic Clinic between April and July 2019. This study was approved by the Bioethics Commission of the Medical University. Written informed consent was obtained from all participants.

Participants

A total of 173 Eastern European women were enrolled in this study. The participants were in good general condition and aged between 20 and 30 years, with a normal body mass index of 18.5–24.9. The participants had never been pregnant. They declared regular menstruation every 28–30 days or taking hormonal combined contraceptives (monophasic combined oral contraceptives) for at least 4 months. The inclusion criteria included Angle Class II with mesial rotation of teeth 16 and 26, confirmed by intraoral scanning, and the absence of acute carious lesions and chronic inflammation in the oral cavity. The exclusion criteria included nicotinism, past orthodontic treatment with fixed appliances, missing teeth, hypodontia, and reduced periodontal bone level, confirmed by an orthopantomogram. Fig. 1 shows the study selection criteria.

This study focused on cases of Angle Class II. The selection of such cases allowed for obtaining precise results and excluding potential confounders. For example, a crossbite in the upper first molars can complicate tooth derotation. Adults with a Class II malocclusion can be treated with orthodontic camouflage and non-extraction treatment by moving the upper teeth to the back. In Class II patients, the first molars are rotated medially and lingually. According to the orthodontic treatment recommendations for adults, correcting this rotation is necessary to obtain a correct bite with the lower first molar, moving the buccal cusps backward. It improves occlusal relations and creates a mesial space between the molars. All women who required conservative, periodontal, or surgical treatment during the initial examination were referred to dentists, and women with irregular menstruation were referred to a gynecologist.

Assuming that three groups will be tested (three moments in the cycle) and considering a standard deviation of 0.06, the minimum number of patients in each group should be 29 to obtain a test power of 0.9. Considering a possible dropout, a sample size of 30 patients for each group was considered adequate [2].

Methods

An intraoral scanner was used to obtain precise measurement results. Specially crafted bands (Fig. 2) were positioned on teeth 16 and 26 in all patients to measure tooth mobility throughout testing.

Based on the information obtained from the medical interview, the patients were divided into two groups: the study group (A), which included women who were menstruating, and the control group (B), which included those who were taking hormonal supplements. Women in group A were assigned to three subgroups according to the timing of orthodontic force application: A1 (menstruation), A2 (ovulation phase), and A3 (luteal phase) (Table 1). Each patient received detailed instructions regarding the date of visits and use of the orthodontic appliance.

On examination day I, always at 7:00 a.m., a single venous blood sample from the cubital fossa was collected from patients in groups A and B to determine the progesterone and estrogen levels in the blood and evaluate the hypothalamic–pituitary–ovarian axis, which was analyzed by a gynecologist. The mobility of teeth 16–26 in the sockets was objectively assessed using the Periotest device. Periotest consists of a head that taps the test object and a mechanism that measures the deflection and decrease in speed. The device converts the contact time into a numerical value, which is referred to as the periotest value (PTV). The PTV ranges from −8 to +50. The higher the PTV, the greater the mobility of the examined object [9–14]. The Periotest device is a reproducible tool that can be trusted to carry out the tooth mobility readings accurately [15]. Periotest measurements were conducted three times, and the average value was calculated for each tooth. In the last stage, the bands on teeth 16 and 26 were connected using a transpalatal arch (TPA) made of steel wire with a diameter of 0.8 mm, passive in the transverse, sagittal, and vertical dimensions, TPA was attached to the tube molar band and secured with steel ligatures. The free ends of the TPA were activated at an angle of 45° by measuring the activation with a protractor (Fig. 3a). The positions of teeth 16 and 26 before TPA activation (examination I) and after TPA activation (examination II) were recorded using a scanner. On the scans taken during the examination I, the tops of the proximal buccal cusps of teeth 16 and 26 were marked as mb16 and mb26, respectively, and pictures were taken to ensure that the markings would be reproducible on subsequent scans. The distances between mb16 and mb26 were then measured to determine the intermolar width (M^1).

In examination II, the mobility of the upper teeth was assessed (PTV^2) using Periotest according to the scheme from examination I. Then, the locations of points mb16 and mb26 were noted on successive scans as mb16′ and mb26′. The intermolar width (M^2) was measured. The scans from

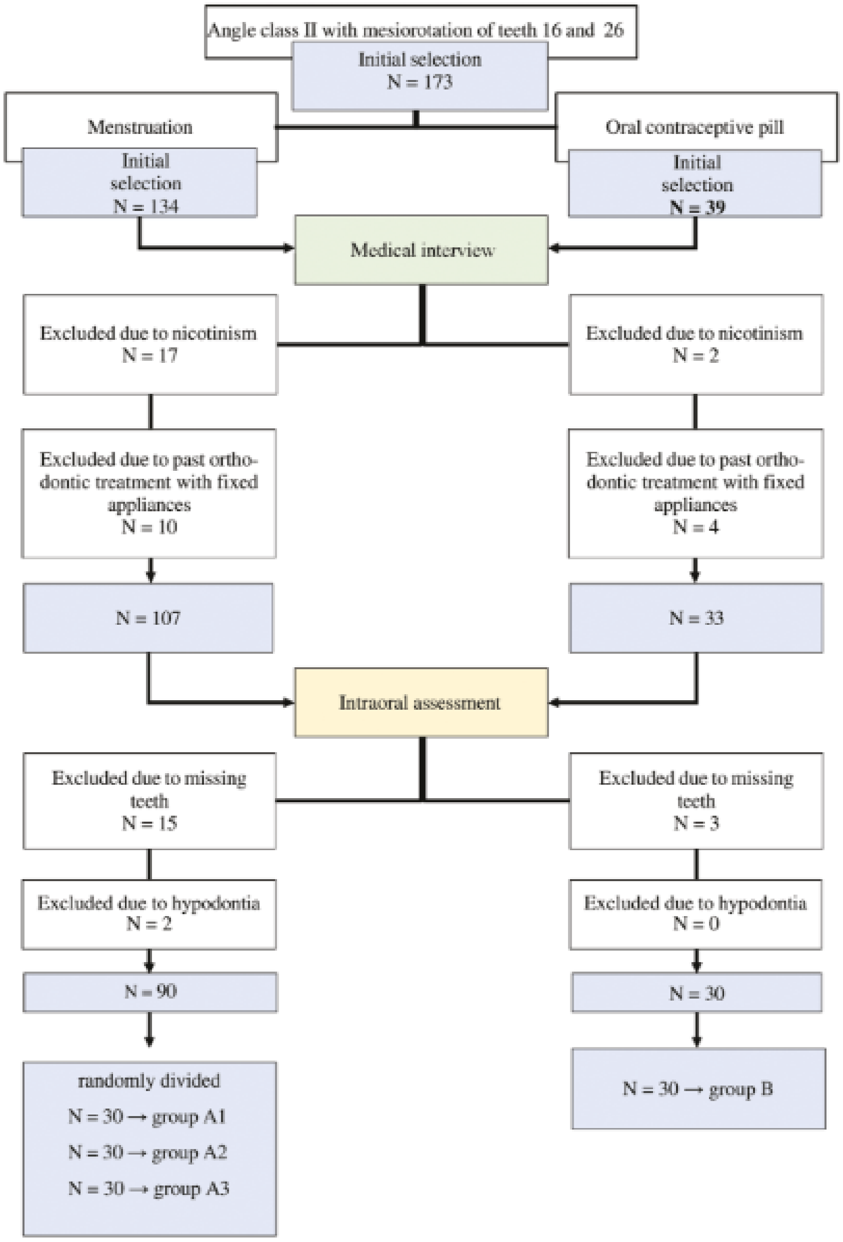

Figure 1. Flowchart of the selection process of the study participants.

examinations I and II were superimposed relative to the center of the anterior–posterior central groove of teeth 16 and 26 to measure the derotation of teeth 16 (O16 = mb16′ – mb16) and 26 (O26 = mb26′ – mb26) and an increase in intermolar width (M^2–M^1) obtained as a result of TPA (Fig. 3b).

Statistical analysis

Statistical analysis was performed using Statistica 13 (TIBCO Software Inc., Palo Alto, CA, USA). The normality of the distribution of continuous variables was tested using the Shapiro–Wilk test. Comparisons of tooth mobility were performed using the Friedman ANOVA test, and post hoc analysis was performed using the Wilcoxon test. Multiple comparisons were performed with Bonferroni correction. The mobility of teeth was compared between groups A and B using the Mann–Whitney *U* test. The mobility of individual teeth was analyzed using the Kruskal–Wallis non-parametric ANOVA test, and multiple comparisons of mean ranks were performed to evaluate it in the context of differences between individual teeth. The Statistica 13.3 power analysis module was used. For one-way ANOVA Statistica demands a significance level of alpha (0.05), assumed power (0.9), number of groups [3], population standard deviation (0.06), and means for each group set to 0, 1, 0.1, and 0.15. The level of statistical significance was set at $P = 0.05$ for each test.

Error method study

Scans

Recordings of $n = 120$ patients were performed by two operators on two occasions, with an interval of approximately 10 min (using scans that could always be recalled). The standard error of the mean difference (SE) was calculated using the formula $SE = \sqrt{\sum_{i=1}^{n} d_i^2/n}$, where d is the difference between the recordings of the individual. The marking SE was 0.0171 mm in O16 and 0.0156 mm in O26. A paired t-test was performed and no significant systematic difference was found at the 5% confidence level between the two recording occasions.

Figure 2. The design of a band especially adapted to the aim of our study. The "window" enables the application of Periotest to the tooth (at the cross).

Superimposition

Superimposing the scans from examinations I and II relative to the center of the anterior–posterior central groove (single point) may be regarded as another limitation of the study. Superimposing an image on soft tissue may be controversial [16], but use hard tissue [17], that is, incisor surfaces, it can be clearly stated that this test has no measurement error because all error factors have been eliminated to a minimum [18, 19].

Results

A total of 120 women between the ages of 20 and 30 years were included in this study. Since the clinical data were obtained by dividing the patients into groups based on their medical history, the menstrual cycle hormone levels were measured in each case to rule out the possibility that patients incorrectly determined the study's start time. Thus, the reliability of the research group assignments was assessed in conjunction with the hormone level test results (Table 2).

Table 1. Scheme of research and division into groups.

	Group			
Study component	A1	A2	A3	B
I (H + PTV[1] + F + M[1])	Menstruation phase: third day of cycle.	Ovulation phase: on the day of ovulation.	Luteal phase: 7 days after ovulation.	Any day
II (PTV[2] + M[2] + O16 + O26)	6 weeks after examination I.			

H, determination of hormone levels; PTV, tooth mobility assessment during examinations I (PTV[1]) and II (PTV[2]); M, intermolar width measurement during examinations I (M[1]) and II (M[2]); F, activation of the orthodontic appliance; O, measurement of tooth derotations 16 (O16) and 26 (O26).

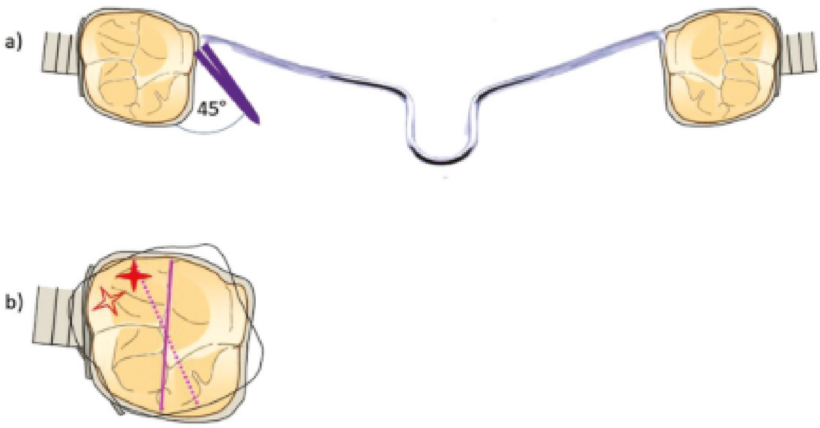

Figure 3. Scheme of (a) activation and (b) superimposition. The dashed line and unfilled starlet indicate the central sulcus and mesial buccal cusp tip of the derotated molar.

Table 2. Sex hormone levels observed in women physiologically [39, 40] and during this study.

Group	Physiological		During this study					
	Progesterone (ng/ml)	Estrogen (pg/ml)	Group	Progesterone (ng/ml)		Estrogen (pg/ml)		Age of women in study (years)
				Median	Quartiles	Median	Quartiles	
Menstruation phase	0.63–0.879	87–132	A1	0.64	(0.51–0.70)	81.40	(73.53–94.50)	21 $^{5}/_{12}$–26 $^{11}/_{12}$
Ovulation phase	1.25–6.3	130–330	A2	2.50	(1.72–4.13)	136.41	(128.42–224.90)	21 $^{9}/_{12}$–27 $^{7}/_{12}$
Luteal phase	3.81–21.7	93–150	A3	13.00	(11.30–19.30)	128.00	(102.00–139.50)	22 $^{5}/_{12}$–27 $^{3}/_{12}$
Oral contraceptives	0.05–0.116	254–290	B	0.05	(0.05–0.10)	231	(222.00–239.50)	23 $^{7}/_{12}$–25 $^{1}/_{12}$

In all groups, progesterone and estrogen levels were within the normal ranges related to the phase of the cycle or hormonal supplementation. Statistically significant differences in the levels of both hormones were observed between the groups ($P < 0.001$), which confirmed the self-discipline of the patients and the reliability of the division of the study participants. In group A, the average interval between periods was 27.64 days and was statistically comparable ($P > 0.05$).

Tables 3–5 show the results of the descriptive statistics of tooth mobility in the sockets in examinations I and II. The difference between PTV^2 and PTV^1 and the change in tooth mobility following appliance activation varied between the groups. However, the responses of the first premolars, canines, and incisors to appliance activation were similar ($P = 0.57$). Since the change in the mobility of the first premolars was only observed during the activation of the appliance 7 days after ovulation, only the change in the mobility of teeth 15, 16, 25, and 26 in all study groups was subjected to further analysis (Table 5).

After 6 weeks from TPA activation (examination II), teeth 16 and 26 moved in all study groups (Table 6). Group B showed the smallest displacement, similar to group A2 ($P = 0.64$), in which the force was applied at the time of ovulation. The values of parameters O16, O26, and M^2-M^1 were the highest in group A3, indicating the best efficiency of TPA, whereas they were lower in group A1 but still greater than those in the control group. These intergroup differences were statistically significant ($P < 0.001$).

Discussion

Numerous studies have been conducted on the influence of estrogen and progesterone on tooth movement. However, these studies were animal experiments, and their findings cannot be generalized to humans due to the vast differences in anatomy and physiology between animals and humans. Animal experiments should be conducted in consultation with veterinarians, who can help researchers choose the appropriate animal model based on their clinical knowledge [20, 21]. This justifies the selection of patients for our study. However, because the homogeneity of the material is the foundation for material reliability, it was the primary criterion for inclusion in our study. Therefore, participants were of similar age, had a statistically comparable average interval between periods, and had their blood obtained at a set time over the months of April–July. In this way, the influence of factors, such as age, time of day, and season, on the test results was excluded. European women have their first menstrual period at the age of 9–16. According to the Lauritzen scale, sexual maturity in girls is assessed 3–5 years after the first menstruation. By qualifying women aged between 20 and 30 years for this study, we ruled out ovulation disorders, specifically lack of ovulation resulting in low progesterone levels, a characteristic of both teenagers and women in the perimenopausal period [22–24]. Finally, the effect of nicotinism on PDL metabolism was removed by excluding female smokers from the study [25, 26]. Furthermore, it is notable that nicotine lowers estrogen levels [27].

Accurate presentation and explanation of the hormonal menstrual cycle and changes that occur in various phases allowed the participants to understand the importance of attending the visit for TPA activation at the specific time assigned to each group. This awareness and discipline of women were reliably and objectively confirmed by assessing hormone levels in examination I.

The use of Periotest as a measurement instrument was also fully justified. Periotest is widely accepted and used to measure mobility *in vivo* and *in vitro* in periodontology, implantology, orthodontics, and traumatology. Periotest has the advantages of ease of use, ability to perform horizontal and vertical measurements, and repeatability of results [9–12]. Therefore, this study can be replicable in any research center and even in dental practices.

The range of PTV measured in our tests was from −8 to +19 [28], which is evidence of tooth stability. Therefore, we have proved that changes caused by orthodontic appliances, specifically TPA activated at an angle of 45°, do not lead to pathological tooth mobility in the alveoli. These findings are contrary to those reported by Yee *et al.*, who showed that, under the effect of orthodontic stress and as a result of establishing a zone of compression and bone resorption, which widens the periodontal space, tooth mobility reached the second or even third degree [29]. During our research, the mobility was within the first degree, which means that the rotation of teeth 16 and 26 with TPA does not have a destructive effect on young and healthy periodontium. The luteal phase of the menstrual cycle and menstruation are characterized by increased mobility of teeth embedded in the sockets, even in the absence of a mechanical load [2]. However, the lack of pathological mobility is caused, among other things, by hormonal factors, in which estradiol slows down bone resorption, whereas progesterone stimulates bone formation [30].

Since the tooth movements measured had a small range, it was necessary to use a scanner with an accuracy of 20 microns to assess displacement as small as 0.01 mm. Using the scanner, significantly less tooth displacement was observed

Table 3. PTV[1] by study group. The Kruskal–Wallis ANOVA test was used to compare mobility (measured using Periotest during the first examination) between teeth. The findings showed that some teeth exhibited significantly higher PTV than others, regardless of the study group.

	PTV[1]							
	A1		A2		A3		B	
Tooth	Median	Quartiles	Median	Quartiles	Median	Quartiles	Median	Quartiles
16	0.0	(−0.3,0.0)	0.2	(0.1,1.0)	1.8	(1.1,2.3)	0.6	(0.15,1.3)
15	1.0	(0.4,2.0)	1.1	(0.6,2.1)	1.2	(0.8,2.5)	1.2	(0.7,2.05)
14	1.0	(0.3,2.1)	1.0	(0.3,2.1)	1.1	(0.4,2.2)	1.1	(0.6,2.1)
13	−0.1	(−0.2,0.1)	−0.1	(−0.2,0.1)	0.1	(0.0,0.3)	−0.1	(−0.5,0.1)
12	2.1	(1.5,3.0)	2.1	(1.6,3.0)	2.2	(1.7,3.1)	2.2	(1.6,3.25)
11	2.0	(1.2,2.8)	2.0	(1.2,2.8)	2.1	(1.3,3.2)	2.1	(1.3,3.4)
21	2.1	(1.2,2.7)	2.1	(1.2,2.7)	2.2	(1.3,2.8)	2.1	(1.2,3.15)
22	2.0	(1.4,3.0)	2.0	(1.4,3.0)	2.1	(1.5,3.1)	2.0	(1.35,3.25)
23	−0.1	(−0.2,0.0)	−0.1	(−0.2,0.1)	0.0	(0.0,0.2)	−0.2	(−0.45,0.1)
24	1.0	(0.3,2.1)	1.0	(0.3,2.1)	1.0	(0.4,2.2)	1.0	(0.5,2.0)
25	1.0	(0.4,2.0)	1.0	(0.4,2.0)	1.1	(0.6,2.1)	1.1	(0.75,2.15)
26	0.1	(0.0,0.5)	0.5	(0.1,1.0)	1.5	(1.0,2.8)	0.6	(0.2,1.1)
P value	<0.001		<0.001		<0.001		<0.001	

Table 4. PTV[2] by study group. The Kruskal–Wallis ANOVA test was used to compare mobility (measured using Periotest during the first examination) between teeth. The findings showed that some teeth exhibited significantly higher PTV than others, regardless of the study group.

	PTV[2]							
	A1		A2		A3		B	
Tooth	Median	Quartiles	Median	Quartiles	Median	Quartiles	Median	Quartiles
16	5.9	(4.5,7.0)	7.1	(5.4,8.6)	9.8	(6.9,12.3)	4.9	(2.9,6.75)
15	3.1	(2.0,4.0)	4.3	(3.2,6.3)	5.5	(4.0,7.2)	2.7	(1.8,3.6)
14	1.0	(0.5,2.9)	1.1	(0.9,3.0)	1.6	(1.0,3.2)	1.1	(0.6,2.0)
13	−0.1	(−0.2,0.1)	−0.1	(−0.2,0.2)	0.0	(0.0,0.2)	0.0	(−0.3,0.15)
12	2.2	(1.6,3.1)	2.2	(1.6,3.2)	3.3	(2.8,4.0)	2.2	(1.6,3.25)
11	2.1	(1.2,3.0)	2.1	(1.3,3.1)	2.1	(1.3,3.2)	2.1	(1.4,3.45)
21	2.1	(1.3,2.8)	2.1	(1.2,2.8)	2.1	(1.4,3.2)	2.1	(1.2,3.15)
22	2.0	(1.4,3.1)	2.0	(1.4,3.1)	2.2	(1.5,3.1)	2.0	(1.35,3.25)
23	−0.1	(−0.2,0.1)	0.0	(0.0,0.4)	0.0	(0.0,0.2)	0.0	(−0.2,0.1)
24	1.0	(0.5,2.1)	1.1	(0.7,2.9)	1.4	(0.8,3.2)	1.1	(0.6,2.0)
25	2.5	(1.2,3.2)	3.8	(2.5,5.9)	4.6	(3.4,6.6)	3.1	(2.1,4.05)
26	6.0	(4.8,7.2)	7.2	(5.6,8.9)	7.9	(6.1,11.0)	4.7	(3.05,6.7)
P value	<0.001		<0.001		<0.001		<0.001	

Table 5. Changes in the mobility of teeth 15, 16, 25, and 26 under the influence of TPA by study group. The Kruskal–Wallis ANOVA test was used to compare changes checking whether the mobility change of the four most mobile teeth differs among groups A1, A2, A3, and B. The difference in mobility was observed vary by group for all four teeth.

	PTV[2]-PTV[1]								
	A1		A2		A3		B		
Tooth	Median	Quartiles	Median	Quartiles	Median	Quartiles	Median	Quartiles	*P* value
16	5.9	(4.5, 7.2)	6.9	(5.1, 9)	8.0	(5.4, 11)	4.3	(2.3, 6.05)	<0.001
26	5.9	(4.8, 7.2)	6.7	(5, 8.8)	6.4	(4.7, 9)	4.1	(2.3, 6.3)	<0.001
15	2.1	(0.5, 3)	3.2	(1.8, 5)	4.3	(2.5, 5.4)	1.5	(0, 2.25)	<0.001
25	1.5	(0.2, 2.7)	2.8	(0.8, 4.6)	3.5	(1.9, 5)	2.0	(0.15, 3.05)	<0.001

Table 6. Orthodontic parameters with descriptive statistics in all study groups. Intermolar width (in mm) and rotation of teeth 16 and 26 by study group.

	Measurement (mm) of the average minimum and maximum value							
	A1		A2		A3		B	
Parameter (mm)	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
M^1	54.58	54.49–54.67	54.56	54.46–54.60	54.56	53.46–54.65	54.57	54.48–54.65
M^2	54.64	54.51–54.67	54.60	54.55–54.60	54.60	54.57–54.61	54.63	54.53–54.61
O16	0.23	0.21–0.25	0.13	0.12–0.14	0.29	0.27–0.30	0.11	0.08–0.14
O26	0.23	0.21–0.25	0.15	0.14–0.17	0.29	0.27–0.30	0.11	0.07–0.14
M^2–M^1	0.06	0.04–0.18	0.04	0.10–0.14	0.04	0.04–0.19	0.05	0.05–0.09

M: intermolar width in study I (M^1) and II (M^2); O: 16 (O16) and 26 (O26) rotation.

in the group of women taking oral contraceptives (group B) than in the group of women with regular menstruation (group A). This can be attributed to the non-physiological levels of estrogen. Its deficiency contributes to osteoporosis, as its decrease triggers a cascade of cytokines, the most important of which is the RANK-L signaling pathway that stimulates rapid bone growth and resorption [31]. This indicates that hyperestrogenism-inducing contraceptive pills, such as testosterone, stimulate bone growth [32, 33], which explains why the teeth of 16 and 26 in women taking oral contraceptives were significantly less susceptible to the force of TPA than those in women with physiologically fluctuating estrogen levels. Long-term use of hormonal tablets has been proven to have a stabilizing effect on the teeth during orthodontic treatment, as we have proven in previous studies that women who do not have malocclusion but use contraception have significantly lower tooth mobility than women who are menstruating [2].

The negative correlation between the effectiveness of tooth movements and estrogen shown in our study could theoretically suggest that orthodontic force should be applied during menstruation since estrogen levels decrease during menstruation and increase during ovulation. However, dermatological studies [34–36] have reported that a decrease in estrogen levels causes skin flaccidity, which becomes less elastic. This is due to the effect of estrogen on collagen, which is the scaffolding for the skin, is found in the gingiva, and forms the gingiva and PDL. Furthermore, inflammation may develop due to the reduced proliferation of the epithelial lining in the oral cavity under the influence of this hormone. The increase in tooth mobility during menstruation could be due to the ease of injury of the dry mucosa and the reduced tension of the ligaments. In addition, coagulation tests explain why wounds heal worse during menstruation and why thrombosis may occur while taking hormonal contraception [37]. These findings indicate that activating TPA during the menstrual phase may result in periodontal damage that the body cannot repair. The fact that tooth mobility in the alveoli is determined not only by estrogen but also by progesterone is still a matter of debate [31, 38–40]. Since no study has been conducted to investigate the impact of female hormones on tooth mobility, we compared our findings with those of orthopedic studies, which assessed the impact of female hormones on the skeleton and ligament system, indicating that progesterone reduces ligament stiffness [41]. In addition, body temperature increases by 0.2°C–0.5°C under the influence of progesterone. This increase facilitates the passage of the RANK-L cascade pathways, thereby facilitating tooth movement under the influence of orthodontic force. Notably, the increase in the amount of fluid in the periodontal space associated with water retention in the body in the last phase of the menstrual cycle [42] also contributes to the increase in tooth mobility in the sockets.

Understanding the influence of estrogen on the mechanical movement of teeth can help shorten the treatment time, especially since its prolongation has negative side effects in the form of enamel demineralization and periodontal diseases [43]. Therefore, clinicians have directed their efforts for years toward developing methods to accelerate tooth movement under the influence of orthodontic forces. These methods include Wilckodontics [44] or reducing the friction between the bracket and slot using self-ligating brackets and loosely twisted steel ligatures. Furthermore, understanding the impact of menstrual cycle hormones on the efficiency of orthodontic treatment helps take a completely innovative approach to activating the braces. It enables one to choose the optimal time to apply orthodontic force to accelerate tooth movement and reduce treatment time. Moreover, our findings that tooth mobility in alveoli significantly increases twice during the menstrual cycle (groups A1 and A3) support the need to strengthen the anchorage during the distalization of teeth 15 and 25 after the derotation of teeth 16 and 26, whose stability is not protected when estrogen levels fluctuate. In addition, strengthening the anchorage contributes to shortening the treatment duration [45].

Based on information on the behavior of the tooth and its PDL under the influence of hormones of the menstrual cycle and orthodontic force load, we can conclude that the moment of the cycle at which progesterone dominates (group A3) is the most desirable for TPA activation. Menstruation following the luteal phase is associated with decreased estrogen levels, facilitating tooth movement, partially due to increased osteoclast activity. Changes in collagen structure induced by a decrease in estrogen levels cause capillaries to break, resulting in increased bone resorption, which is most desirable 14 days after TPA activation. Therefore, TPA activation in the luteal phase, when progesterone raises the body temperature, softens the ligaments, and dilates the vessels, enabling delicate tissue regeneration and subsequent bone resorption 2 weeks later under the influence of estrogen secreted during menstruation, has a positive effect not only on the effectiveness but also on the long-term results of orthodontic treatment.

Based on the study findings, the increased resorption of the alveolar process or the alveolar part of the mandible may be caused by the activation of an appliance at the time of ovulation. Thus, further studies are needed to investigate this.

The study has several limitations, a power analysis for three main measured parameters: scope of rotation of tooth 16 and 26 (parameter O), changes in mobility of tooth 16 and 26 before and after activation (PTV2-PTV1 parameter) and difference between intermolar width in study I and II (M2-M1 parameter), was performed to check the power of the conducted statistical tests. For ANOVA test for scope of rotation and change of mobility, we achieved a power >0.99, but for intermolar width change power equals 0.68.

Conclusions

Class II treatment in young women should be preceded by a medical history, including information on menstruation. This makes it possible to not only activate the appliance on a specific day of the cycle but also explain to patients taking birth control how it can potentially slow down tooth movement and prolong treatment. Based on our research on the qualification and quantification of changes in tooth mobility in the sockets during the menstrual cycle and orthodontic treatment, it was possible to establish that female sex hormone levels significantly correlate with the efficacy of tooth movements. Therefore, the moment of appliance activation should be optimally selected during the luteal phase of the menstrual cycle to increase the effectiveness of orthodontic treatment and reduce its complications.

Women in the ovulation phase and those taking contraceptives containing high amounts of estrogen exhibit similar clinical behavior. The findings of this study suggest that activation should ideally be carried out during the luteal and menstrual phases when estrogen levels are typically low and greater tooth movement is likely to occur. Furthermore, women using contraceptives are likely to be less susceptible to orthodontic surgery, although their treatment duration may be slightly longer.

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Author contributions

Małgorzata Peruga (Conceptualization [Lead], Data curation [Supporting], Formal analysis [Supporting], Investigation [Supporting], Methodology [Lead], Project administration [Lead], Resources [Lead], Software [Lead], Supervision [Supporting], Validation [Lead], Visualization [Lead], Writing—original draft [Lead], Writing—review & editing [Supporting]), and Joanna Lis (Data curation [Lead], Formal analysis [Lead], Investigation [Lead], Supervision [Lead], Validation [Lead], Writing—review & editing [Lead])

Conflicts of interest

None declared.

Data availability

Not applicable.

Institutional review board statement

This study was approved by the Bioethics Commission at the Medical University in Wrocław, no. 788/2018, approval date: 27 December 2018.

Informed consent statement

Patients were informed that participation in the exam was voluntary, and they provided their written consent to all tests. The confidentiality and privacy of participants have been respected.

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2. Informacja o indywidualnym wkładzie współautorów.

Wrocław, dnia 12.05.2024 r.

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OŚWIADCZENIE WSPÓŁAUTORA

1. Peruga Małgorzata, Beata Kawala, Michał Sarul, Jakub Kotowicz, Joanna Lis. Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics?" *Animals* 2023; 13(4):629. https://doi.org/10.3390/ani13040629

   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na recenzji i redakcji oraz na nadzorze.

Podpis

Przemyśl, dn. 4.05.2023 r.

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OŚWIADCZENIE WSPÓŁAUTORA

1. Peruga Małgorzata, Beata Kawala, Michał Sarul, Jakub Kotowicz, Joanna Lis. Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics?" Animals 2023; 13(4):629. https://doi.org/10.3390/ani13040629

   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na opracowaniu wizualizacji.

Podpis

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1. Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego.
   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na metodologii, analizę formalnej, weryfikacji danych, recenzji i redakcji, nadzorze , oraz administracji projektu.

2. Are currently selected laboratory animals useful in the research of how female hormones influence orthodontic biomechanics?
   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na metodologii, analizę formalnej, weryfikacji danych, recenzji i redakcji, nadzorze , oraz administracji projektu.

3. The impact of progesterone and estrogen on the tooth mobility.

   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na konceptualizacji, metodologii, oprogramowaniu, walidacji, analizie formalnej i danych, przygotowaniu projektu oryginalnego, recenzji i redakcji, wizualizacji, nadzorze.

4. Correlation of sex hormone levels with orthodontic tooth movement in the maxilla: a prospective cohort study.
   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na konceptualizacji, metodologii, oprogramowaniu, walidacji, analizie formalnej i danych, przygotowaniu projektu oryginalnego, recenzji i redakcji, wizualizacji, nadzorze.

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Zakład Metod Matematycznych

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OŚWIADCZENIE WSPÓŁAUTORA

1. Peruga Małgorzata, Joanna Piwnik, Joanna Lis. The Impact of Progesterone and Estrogen on the Tooth Mobility Medicina 2023; 59(2):258. https://doi.org/10.3390/medicina59020258

   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na analizie danych statystycznych.

Joanna Piwnik

Podpis

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OŚWIADCZENIE WSPÓŁAUTORA

1. Peruga Małgorzata, Beata Kawala, Michał Sarul, Jakub Kotowicz, Joanna Lis. Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics?" *Animals* 2023; 13(4):629. https://doi.org/10.3390/ani13040629

   Oświadczam, że mój indywidualny wkład w powstanie powyższego artykułu polegał na recenzji i redakcji oraz na nadzorze.

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3. Opinie komisji bioetycznej

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 788/2018

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

dr hab. Jacek Daroszewski (endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód (duchowny)
mgr Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
dr hab. Leszek Szenborn (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Wpływ zmiany stężenia hormonów podczas cyklu miesiączkowego na tempo przesunięć ortodontycznych"

4.

zgłoszonym przez **lek. med., lek. dent. Małgorzatę Perugę** zatrudnioną w Małgorzata Peruga Indywidualnej Praktyce Lekarskiej w Łodzi oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w Małgorzata Peruga Indywidualnej Praktyce Lekarskiej w Łodzi pod nadzorem prof. dr hab. Joanny Antoszewskiej **pod warunkiem zachowania anonimowości uzyskanych danych**.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu

Opinia powyższa dotyczy: projektu badawczego będącego podstawą rozprawy doktorskiej

Wrocław, dnia 27 grudnia 2018 r.

BW

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący

prof. dr hab. Jan Kornafel

4. Wykaz publikacji autora

Publikacje w czasopismach bez IF:

1. Agnieszka Nawrocka, Grażyna Śmiech-Słomkowska, **Małgorzata Peruga**, Maciej Borowiec: Dysplazja zębiny typu 1- przegląd piśmiennictwa i opis dwóch przypadków. *Stomatologia współczesna* 2016, 23, 4, s. 16-26.

   Pkt. MNiSW/KBN: 4

2. **Małgorzata Peruga,** Joanna Jacaszek, Aleksandra Oleszczak, Grażyna Śmiech-Słomkowska: Znaczenie dokładnego badania przedmiotowego i podmiotowego w prawidłowej ocenie wad rozwojowych. Drożny przewód nosowo-podniebienny -opis przypadku. *Ortodoncja w praktyce*, 2017, 1, s. 23-33.

   Pkt. MNiSW/KBN: 5

3. **Małgorzata Peruga**: Przegląd etiologii diastem i trem – doświadczenia własne. *Ortodoncja w praktyce*, 2017, 4, s. 7-21.

   Pkt. MNiSW/KBN: 5

4. **Małgorzata Peruga**, Konrad Małkiewicz: Rana postrzałowa policzka- opis przypadku. *e-Dentico,* 2018, 3, 71, s. 102-8.

   Pkt. MNiSW/KBN: 6

5. **Małgorzata Peruga**, Joanna Antoszewska-Smith: Ortodontyczny ruch zęba a zmiana poziomów hormonów podczas cyklu miesiączkowego. *Ortodoncja w praktyce*, 2018, 4, s. 23-27 i 63-64.

   Pkt. MNiSW/KBN: 5

6. Klaudia Bura, Iza Leśniewska, **Małgorzata Peruga,** Krzysztof Kamiński, Aleksandra Oleszczak: Mikrodoncja– opisy przypadków i leczenie. *Ortodoncja w praktyce*, 2020, 4.

Pkt. MNiSW/KBN: 5

7. **Małgorzata Peruga**, Joanna Lis: Horyzontalnie położony ząb sieczny boczny górny. Opis przypadku, *Ortodoncja w praktyce*, 2022, 2.

Pkt. MNiSW/KBN: 5

8. **Małgorzata Peruga**, Grzegorz Piątkowski, Joanna Jacaszek: Zastosowanie asymetrycznego aparatu RPE (rapid palatal expansion) ze śrubą wachlarzową u pacjenta z jednostronnym rozszczepem wargi i podniebienia – opis przypadku. *Ortodoncja w praktyce*, 2023, 1.

Pkt. MNiSW/KBN:5

9. Joanna Jacaszek, Sebastian Jamrozik, Marcelina Grochowska, **Małgorzata Peruga:** Zespół taśm owodniowych - opis przypadku i przegląd piśmiennictwa. *Twój Przegląd Stomatologiczny*, 2023, 6.

Pkt. MNiSW/KBN: 5

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1. **Małgorzata Peruga**, Piątkowski Grzegorz, Kotowicz Jakub, Joanna Lis: Orthodontic Treatment of Dogs during the Developmental Stage: Repositioning of Mandibular Canine Teeth with Intercurrent Mandibular Distoclusion. *Veterinary Sciences*, 2022, 9, 8: 392.
   https://doi.org/10.3390/vetsci9080392

   Pkt. MNiSW/KBN: 20

   IF: 2,518

2. **Małgorzata Peruga**, Joanna Piwnik, Joanna Lis: The Impact of Progesterone and Estrogen on the Tooth Mobility. *Medicina*, 2023, 59, 2: 258. https://doi.org/10.3390/medicina59020258

   Pkt. MNiSW/KBN: 20

   IF: 2,948

3. **Małgorzata Peruga,** Michał Sarul, Jakub Kotowicz, Beata Kawala, Joanna Lis. Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics? *Animals*, 2023, *13*, 4: 629.
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   Pkt. MNiSW/KBN: 100

   IF: 3,213

4. **Małgorzata Peruga,** Joanna Lis, Correlation of sex hormone levels with orthodontic tooth movement in the maxilla: a prospective cohort study. *European Journal of Orthodontics*, 2024, 46, cjae025.
   https://doi.org/10.1093/ejo/cjae025

   Pkt. MNiSW/KBN: 140

   IF: 2,6

Streszczenia i publikacje książkowe:

1. **Małgorzata Peruga**, Monika Sokołowska „Stomatologiczne potrzeby leczenia u dzieci niepełnosprawnych"- XVIII Michał Kłopotowski Scientific Dental Student Conference 21st April 2012, Łódź.

2. **Małgorzata Peruga**, Monika Sokołowska „Stomatologiczne potrzeby leczenia u dzieci niepełnosprawnych", Stomatologia współczesna 2012, vol. 19, nr 2, s. 89.

   Pkt. MNiSW/KBN: 3

3. Łukasz Sokołowski, **Małgorzata Peruga**, Piotr Nowak H_2O_2 concentration in exhaled breath condensate does not differ between maintenance hemodialysis patients, kidney transplant recipients and healthy controls unless adjusted for DLCO: a preliminary study JUVENES PRO MEDICINA, Łódź 2015- miejsce drugie w sekcji internistycznej JUVENES PRO MEDICINA

4. Grażyna Śmiech- Słomkowska**, Małgorzata Peruga:** Znaczenie mięśni w budowie i czynnościach narządów jamy ustnej. Logopedia wobec wyzwań i zagrożeń XXI. Łódź, 14 października 2017 r.; Łódź: Wydawnictwo Uniwersytetu Łódzkiego 2018, s. 29-33.

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5. **Małgorzata Peruga,** Joanna Jacaszek, Aleksandra Oleszczak, Grażyna Śmiech-Słomkowska: Znaczenie dokładnego badania przedmiotowego i podmiotowego w prawidłowej ocenie wad rozwojowych. Drożny przewód nosowo-podniebienny – opis przypadku, Ortodoncja w praktyce – teksty wybrane Tom I, Elamed, Katowice 2019, s. 264-72.

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6. **Małgorzata Peruga**: Przegląd etiologii diastem i trem – doświadczenia własne, Ortodoncja w praktyce – teksty wybrane Tom I, Elamed, Katowice 2019, s.273-95.

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7. **Małgorzata Peruga,** Michał Sarul, Jakub Kotowicz, Beata Kawala, Joanna Lis. Are Currently Selected Laboratory Animals Useful in the Research of How Female Hormones Influence Orthodontic Biomechanics? Implementing the 3Rs in Laboratory Animal Research—From Theory to Practice, MDPI, Basel, Switzerland 2023, s. 91-102.

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