THE ASSOCIATION OF ORAL CONTRACEPTIVE AND HORMONAL
REPLACEMENT THERAPY USE WITH PERIODONTITIS

by

Arpit Rajeshkumar Mehta

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Approved by:

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Dr. Larissa R. Brunner Huber

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Dr. Michael E. Thompson

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Dr. Ahmed A. Arif

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ABSTRACT

ARPIT MEHTA. The association of oral contraceptive and hormonal replacement therapy use with periodontitis (Under the direction of DR. LARISSA R. BRUNNER HUBER)

The majority of US women have used oral contraceptives at some point in their lives and approximately 5% have used hormone replacement therapy (HRT). Few studies have investigated the association between these hormonal regimens and periodontitis, and results have been conflicting. The objective of the current study was to determine if women who had ever used oral contraceptives or hormonal replacement therapy had increased odds of periodontitis. This study was a secondary data analysis of 2011-2012 National Health and Nutrition Examination Survey (NHANES) data. Multivariate logistic regression was used to calculate odds ratios and 95% confidence intervals. After adjusting for age, race/ethnicity, income, education, and alcohol use, women who had ever used oral contraceptives had decreased odds of periodontitis, however, the result was not statistically significant (OR=0.74, 95% CI: 0.36-1.50). After adjusting for race/ethnicity, income, education, last dental visit, smoking and marital status, women who had ever used hormonal replacement therapy had slightly increased odds of periodontitis (OR=1.17, 95% CI: 0.55-2.49). The evidence regarding the association between the use of oral contraceptives and periodontitis is conflicting and the evidence regarding the association between hormonal replacement therapy and periodontitis is sparse. Additional research is needed utilizing large, nationally representative samples to determine the true association between these hormone regimens and periodontitis.

Understanding this association can assist dentists and other health care providers in taking better care of women who use these regimens.

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CHAPTER 1: INTRODUCTION

Peridontitis is defined as an "inflammatory disease of the supporting tissues of the teeth caused by specific micro-organisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both" (Carranza, 2002, p. 81). The prevalence of periodontitis in US adults age 30 years and older is estimated to be 47.2% (Eke, Dye, Wei, Thornton-Evans and Genco, 2012). Periodontal disease at an early stage is treated by removing the plaque and calcified plaque (referred to as calculus) by teeth cleaning (scaling and root planning). Advanced periodontal diseases have different treatment modalities which may include surgery. Left untreated, periodontitis leads to loosening and eventually the loss of the tooth.

Nearly 70% of US adults 65 years of age or older have periodontal disease (Eke et al., 2012). Risk factors for periodontitis include smoking, diabetes, infrequent dental visits, previous periodontal disease, stress, reduced dietary intake of calcium, and obesity (Carranza, Newman, Takei, & Klokkevold, 2006, p. 90-91; Nishida et al., 2000; Suvan et al., 2011). Hormonal changes that women may experience, including pregnancy and/or the use of hormonal regimens such as oral contraceptives or hormone replacement therapy (HRT), may be also associated with periodontal disease (Carranza, Newman, Takei, & Klokkevold, 2006, p. 230, p236), however, studies show conflicting evidence and found no association, some showed a positive association and others a negative

association. (Brusca et al., 2010; Haerian-Ardakani et al., 2010; Mullally, Coulter, Hutchinson, & Clarke, 2007; Taichman, & Eklund, 2005).

Given that 82% of US women have used oral contraceptives at some point during their lives (CDC, 2010) and 4.9% of women use HRT (Sprague, Trentham-Diez and Cronin, 2012), further investigating the potential association between the use of these hormonal regimens and periodontal disease is important. This study used nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to evaluate if women who used oral contraceptives or HRT have increased odds of periodontal disease. Research has shown that periodontal disease may influence systemic disease like diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, and acute bacterial pneumonia (Carranza, 2002, p.230). Given the influence of oral health on chronic diseases, identifying other potential risk factors for periodontal diseases in women is important, so that women can be educated and advised of the importance of seeking regular dental care.

CHAPTER 2: LITERATURE REVIEW

2.1. Periodontal Disease and the Periodontium

Chronic periodontitis, formerly called adult periodontitis or chronic adult

periodontitis, is defined as "an infectious disease resulting in inflammation within the

supporting tissues of the teeth, progressive attachment loss, and bone loss" (Carranza,

2002, p. 398). An estimated 47% of US adults (62% men, 38% women) have

periodontitis (Eke et al., 2012). Risk factors for periodontitis include smoking, diabetes,

infrequent dental visits, previous periodontal disease, stress, reduced dietary intake of

calcium, and obesity (Carranza, Newman, Takei, & Klokkevold, 2006, p. 90-91; Nishida

et al., 2000; Suvan et al., 2011).

Periodontitis affects the supporting and investing tissues of the tooth. These

tissues which support the tooth, anchor the tooth to the bone, and constitute the

periodontium, are gingiva, periodontal ligament, cementum, and alveolar bone (Carranza,

Newman, Takei, & Klokkevold, 2006, p. 15). The part of oral mucosa which covers the

alveolus and surrounds the neck of the teeth is called the gingiva, which is more

commonly known as gums (Carranza, Newman, Takei, & Klokkevold, 2006, p. 16).

Alveolar bone, which is also referred to as alveolar process of jaws or alveolus, is the part

of the jaw bone that forms the sockets for teeth and supports the teeth (Carranza,

Newman, Takei, & Klokkevold, 2006, p. 45). The connective tissue that surrounds the

roots of the teeth and connects the teeth to the bone is periodontal ligament (Carranza,

Newman, Takei, & Klokkevold, 2006, p. 36). Cementum covers the roots of the teeth and provides support for the periodontal ligament fibers (Carranza, Newman, Takei, & Klokkevold, 2006, p. 42).

The main clinical and etiologic characteristics of periodontal disease consist of plaque formation, inflammation of periodontium, attachment loss, and alveolar bone loss. Inflammation in the periodontium can extend to the bone and lead to destruction of bone. Eventually this can lead to alveolar bone loss (Carranza, Newman, Takei, & Klokkevold, 2006, p. 354). A V-shaped shallow space encircling the tooth enclosed by the tooth surface on one side and gingiva on the other is the gingival sulcus (Carranza, Newman, Takei, & Klokkevold, 2006, p. 16). When diseased, this sulcus is deepened and is called the periodontal pocket (Carranza, Newman, Takei, & Klokkevold, 2006, p. 336). These pockets are generally formed later in the disease process, however, if gingival recession is present, pockets may be shallow.

2.2. Oral Contraceptives

Although periodontitis is more prevalent among men than women, perhaps due to higher smoking rates among men (CDC, 2015), periodontitis is still a concern among women. One factor that may influence periodontitis among women is the use of oral contraceptives. Oral contraceptives are used by a large proportion of women in the US. According to the Centers for Disease Control and Prevention (CDC), 17.3 % of women use oral contraceptives as their current method of contraception and 82.3% of women have used oral contraceptives at least once in their lives. Modern oral contraceptives contain mainly a low dose of estrogen and progestin (Preshaw, 2013). Oral contraceptives can be classified into three generations based on their introduction in the market

(Preshaw, 2013). First generation oral contraceptives had a high concentration of estrogen, and other contents were norethindrone, ethynodioldiacetate, and lynestrenol, but their use was associated with a high risk of deep vein thrombosis and high blood pressure (Meade, Greenberg, & Thompson, 1980, p. 1157-1161; Meade et al., 1977, p. 948-51). The second generation of oral contraceptives had significantly reduced amount of estrogens and progestins (Preshaw, 2013). In the 1990s, third generation oral contraceptives were introduced and had newer progestins, including norgestimate, gestodene and desogestrel. This generation was developed with the aim to lower androgenic effects of hirsutism and acne (Preshaw, 2013). Third generation oral contraceptives had the same efficacy as second generation oral contraceptives but had fewer side effects such as weight gain, headache, and fluid retention. The issue with the third generation of oral contraceptives began when a series of studies discovered that the risk of venous thrombosis was doubled as compared to second generation oral contraceptives. Modern contraceptives contain levonorgestrel as progestin in combination with ethinylestradiol (Preshaw, 2013).

2.3. Hormonal Replacement Therapy

Another factor that may influence periodontitis in women is the use of hormone replacement therapy (HRT). HRT is usually given to menopausal women and contains estrogen to relieve menopausal symptoms. After the Women's Health Initiative trial in 2002, post-menopausal hormone use declined (Sprague et al., 2012). Approximately, 25% of postmenopausal women used hormones orally in 1999-2000. The use of hormones in 2003-2004 decreased sharply, when the overall use of postmenopausal hormones declined to 11.9% and this prevalence has continued to decrease (Sprague et

al., 2012). According to the most recent data, approximately 5% of women aged 40 years or older used HRT in the year 2010 (Sprague et al., 2012). Women who still have their uterus receive HRT combined with a progestogen for protection of the endometrium (Hickey, Elliott, & Davison, 2012). The estrogen can be administered orally, intravaginally, or transdermally and the progestogen can be administered orally, transdermally, or via an intrauterine device. The estrogen is taken daily, and progestogenis added either in cyclic regimens or daily if it is needed (Roberts, Hickey, Lethaby and Farquhar, 2009). Tibolone is an oral synthetic steroid preparation with estrogenic, androgenic, and progestogenic actions that can also be used as HRT (Hickey, Elliott, & Davison, 2012).

2.4. Studies on use of Oral Contraceptives and Periodontal Diseases

Few studies have investigated the association between the use of oral contraceptives and periodontitis, and the evidence is conflicting regarding the nature of this potential association. A study conducted by Brusca et al. (2010) in Argentina which examined the influence of oral contraceptive use on the occurrence of specific periodontal pathogens subgingivally and the participants' periodontal status had 92 female participants aged 19 to 40 years (oral contraceptive users: n=41 and non-oral contraceptive users: v n=51). Data on oral contraceptive use were collected by a detailed questionnaire and data on periodontitis were obtained by an experienced periodontist. The prevalence of periodontitis among oral contraceptive users was 82.9% and the prevalence of periodontitis among non-oral contraceptive users was 66.7%. The main limitation of this study was the small sample size. Also, since the study was conducted in Argentina, it may not be generalizable to all populations.

A study (Haerlan-Ardakani et al., 2010) comprising of 70 women aged 17 to 35 years who were referred to a periodontal clinic was conducted in Iran. Thirty-five oral contraceptive users (defined as women who used oral contraceptives for a minimum of 2 years) and 35 women who had never taken oral contraceptive pills participated in the study. The periodontal health of these women was assessed by periodontal exam and the use of oral contraceptive was assessed by a questionnaire. The periodontal examination included plaque index, gingival index, probing depth, and attachment level at six sites per tooth. Oral contraceptives users had a significantly higher bleeding index compared to the non-oral contraceptive users ($p<0.0001$). However, there was no significant difference in pocket depth and loss of attachment between the two groups. This study was not able to deduce the duration of time for modern oral contraceptives to produce harmful effects on the periodontium. Also, the study did not take into account the duration of oral contraceptive use, other than defining an oral contraceptive user as a woman who had used them for at least 2 years. Finally, the results of this study may not be generalizable to all populations given that it was conducted in Iran and had a small sample size.

Taichman et al., (2005) performed a cross-sectional study on data from NHANES I and NHANES III. A total of 4,665 pre-menopausal women who were not pregnant and between 17-50 years were selected from the NHANES I and 4,510 women who met the same eligibility criteria were selected from NHANES III. For NHANES I, the data on dental examinations were collected by standardized and trained examiners and they calculated the Periodontal Index (PI). For NHANES III, clinical attachment loss, probing depth, and gingival bleeding were assessed by clinical examination. Oral contraceptive use was assessed by interview questions in both NHANES I and III. This study found a

protective association between current oral contraceptive use and periodontitis after adjustment for confounders, however, this association was only statistically significant for NHANES I (NHANES I: OR=0.36, 95% CI: 0.13-0.96 and NHANES III: OR=0.73, CI: 0.5-1.07). It is important to note that the composition of oral contraceptives has changed since NHANES I and NHANES III were conducted. Oral contraceptives used then had higher estrogen levels as compared to modern oral contraceptives (Taichman et al., 2005).

A cross-sectional study conducted by Mullally et al. in the United Kingdom (2007) considered 50 women between the ages 20 to 35 years. Participants were recruited from general dental clinics between 2001 and 2003 and clinical examinations were performed by calibrated, experienced periodontists. Periodontal examinations included plaque index, gingival index, probing depth, and attachment level at six sites per tooth. Current and previous use of contraceptives, type of pill, and duration of oral contraceptive use was assessed by a questionnaire. Current pill users had deeper mean probing depths compared to non-users (3.3 mm versus 2.7 mm, p=0.017) and more severe attachment loss (2.6 mm versus 1.7 mm, p=0.017). Bleeding on probing sites were higher in oral contraceptive users (44%) as compared to the non-oral contraceptive users (31.1%) (p=0.017). Findings from this study may not be generalizable since this study had a small sample size. Another limitation is that all the participants had clinical evidence of periodontitis as they were recruited from a general dental practice.

2.5. Studies on use of Hormonal Replacement Therapy and Periodontal Diseases

Only one study in the past 10 years has studied the association between HRT and periodontal disease. A clinical trial conducted by Marcos et al. (2005) in Spain had 210

menopausal women aged 40 to 58 years. The aim of this study was to examine the effects of decline in hormones during menopause on oral health. Twenty patients were excluded from this group of women due to other diseases. A total of 134 women received HRT and the other group of 56 women chose not to receive HRT knowing the risks and benefits of the treatment. Patients who were on HRT with estrogen-containing patches received orally administered low-dose progestogen in addition to the patches. Patients who had any dental discomfort were examined by the dentist and their tooth mobility, gingival recession, and probing depths were assessed. Approximately 51.28% of the patients had reduced probing depths. Women undergoing HRT had reduced dental pain, reduced tooth mobility and reduced probing depth of periodontal pockets, indicating that HRT acts as a protective factor for dental pain and periodontal disease. As the study was conducted in Spain and had a small sample size, it may not be generalizable to other populations.

2.6. Possible Biological Mechanism

Women using oral contraceptives show a significant rise in the number of *Prevotella (P. Gingivalis)* species in the gingival micro flora (Saini, Saini and Sharma, 2010). These prevotella species require an essential growth factor naphthoquinones (Saini, Saini and Sharma, 2010). Increased female sex hormones act as a substitute for this growth factor and thus women who are pregnant, or are on oral contraceptives, hormonal replacement therapy, or undergo menopause show an exaggerated response to bacterial plaque which is the etiological factor for causing gingivitis and periodontitis (Saini, Saini, & Sharma, 2010). Also, progesterone and estrogen act as bacterial nutrients. These conditions which lead to increased levels of hormones themselves do not cause gum diseases (gingivitis and periodontitis), they just lead to an exacerbated

response to bacterial plaque. Thus, it is plausible that users of oral contraceptives or HRT may be more likely to have periodontal diseases. However, the exact biological mechanism is unknown. Others have postulated that oral contraceptive users may have a lower risk of periodontitis because they may be more health conscious and have healthier behaviors (Taichman et al., 2005). It is possible that similar healthier behaviors may also extend to HRT users (Krall, Dawson-Hughes, Hannan, Wilson, & Kiel, 1997; Barrett-Connor, 1998; Wilkins, Johansen, Beaudet, & Neutel, 2000).

2.7. Summary and Implications

Few studies have assessed the association between oral contraceptive use and periodontitis. Studies conducted on the potential association between oral contraceptives and periodontitis had small sample sizes and many were conducted internationally (Brusca et al., 2010; Haerlan-Ardakani et al., 2010; Mullaly et al., 2007). In addition, results have been conflicting. Some studies found no association between oral contraceptives and periodontitis (Haerlan-Ardakani et al., 2010) while others found an increased risk of periodontitis among oral contraceptive user (Brusca et al., 2010; Mullaly et al., 2007). One study found a protective association between the use of oral contraceptives and periodontitis (Taichman et al., 2005). Furthermore, data on the association between HRT and periodontitis are sparse. One study found a protective association between the use of HRT and periodontitis (Marcos et al., 2005). However, this study was conducted in Spain and had a small sample size and may not be generalizable to other populations.

The current study investigated the association between the use of oral contraceptives and periodontitis and the association between HRT and periodontitis in a

large, nationally representative sample of women who participated in NHANES. While some studies have found a protective association between oral contraceptives and periodontitis, it is possible that the changing composition of oral contraceptives has now resulted in a harmful association (Saini, Saini and Sharma, 2010). Conversely, it is possible that a protective association between may persist since women who are on hormone regimens are healthier (Krall, Dawson-Hughes, Hannan, Wilson, & Kiel, 1997; Barrett-Connor, 1998; Wilkins, Johansen, Beaudet, & Neutel, 2000). Given that recent evidence suggests that periodontal disease may influence systemic disease like diabetes, stroke, coronary heart disease, chronic obstructive periodontal disease, and acute bacterial pneumonia (Carranza, 2002, p. 230), determining if women who use oral contraceptives or HRT are at increased risk of periodontal disease is important so they can be appropriately evaluated and treated for this condition.

CHAPTER 3: HYPOTHESES

This cross-sectional study investigated the association between the use of oral contraceptives and hormonal replacement therapy and periodontal diseases among women who were participants of the 2011-2012 National Health and Nutritional Examination Survey (NHANES). The following hypotheses were investigated:

1. Women who ever used oral contraceptives have increased odds of periodontal diseases as compared to women who never used oral contraceptives.

2. Women who ever used hormonal replacement therapy have increased odds of periodontal diseases as compared to women who never used hormonal replacement therapy.

CHAPTER 4: METHODS

4.1. Description of NHANES

This cross-sectional secondary data analysis utilized 2011-2012 NHANES data. The National Center for Health Statistics developed NHANES in the early 1960s to collect information on the nutritional status and health of US adults and children (CDC, 2014). NHANES uses interviews and physical examinations to determine the prevalence of diseases and their risk factors. The examination component consists of medical, dental, and physiological measurements and laboratory tests. Before 1999, NHANES was done every 5 years. In 1999, NHANES became a continuous survey, and data are released in two year increments (CDC, 2014).

NHANES uses complex, four stage, probability sampling of non-institutionalized civilians of the US population (Johnson, Dohrmann, Burt and Mohadjer, 2014). During the first stage of the sampling process primary sampling units, which are mostly single counties or groups of small neighboring counties, are selected. The second stage selects the sample of area segments which could be census blocks or a combination of census blocks. In the third stage, Dwelling Units (DUs), are selected and in the fourth stage, individuals within these DUs are selected. Individuals were selected from eligible members of households based on age, sex, income, race, and Hispanic origin. The subsampling was done in such a way that approximate self-weighting samples for each

sub domain could be obtained and the average number of sampled participants per sample household could be maximized (Johnson, Dohrmann, Burt and Mohadjer, 2014).

The sample weight is the estimated number of persons in the target population that a NHANES respondent represents. NHANES sample weights were adjusted for differences in response rates, sampling rates, and coverage rates among persons in the sample, so that accurate national estimates could be obtained. Hispanics, non-Hispanic blacks, Asians, low-income ndividual, and adults aged 80 and over were oversampled by NHANES.

A total of 9,338 individuals participated in the 2011-2012 NHANES. Questionnaires are given to participants at home and in the Mobile Examination Centers (MECs). The overall response rate for the NHANES survey was 72.6% and the response rate among females was also 72.6% (CDC, 2013). The participation rate for the examinations was lower (overall: 69.5% and females: 69.4%) (CDC, 2013). Physical examinations are conducted by medical professionals in the MECs and interviews are conducted in the MECs. Audio computer assisted interviews and computer assisted interviews are administered at MECs, whereas paper administered interviews are conducted at home. The areas that cover more sensitive data, for example, reproductive health and illegal drug use, are administered via Computer Assisted Personal Interviewing (CAPI) system by trained interviewers at MECs. The reproductive health section of the survey contains questions on topics such as menstrual history, pregnancy history, lactation, hormonal replacement therapy use, and oral contraceptive use.

This secondary data analysis was limited to participants who were 30 years of age or older and completed dental examinations. For the oral contraceptive use-periodontitis

association the analysis was further limited to women 30-49 who provided complete information on oral contraceptive use. The HRT-periodontitis analysis was limited to women 50-65 years of age who had complete information on HRT use (National Institute on Aging, 2010).

4.2. Exposure Assessment

Data on use of oral contraceptives and hormonal replacement therapy were self-reported in the reproductive health portion of the questionnaire. Women who indicated that they had ever used oral contraceptives were considered to be exposed to oral contraceptives. For the HRT-periodontitis analysis, women who answered that they had ever used any form of HRT were considered exposed.

4.3. Outcome Assessment

The outcome in this study is periodontal disease and was measured by clinical examination by dentists who were D.D.S. or D.M.D. licensed in at least one U.S. state. The full mouth assessment is done at six sites per tooth and periodontal pockets, recession, and loss of attachment are measured (CDC, 2014). The examiners are calibrated, periodically monitored, and retrained as needed. Data on oral health are entered on a computerized data collection form (CDC, 2014). The data are reviewed systemically for any error or inconsistencies as a part of quality control (CDC, 2014). For this study, periodontitis was defined as having 3 mm or more of attachment loss in at least 2 sites examined. This definition of periodontitis includes the moderate and severe categories of periodontitis (Carranza, 2002, p. 400).

4.4. Covariate Assessment

Confounders considered were based on previous research and are variables associated with the exposure and outcome but not on the causal pathway. The potential confounders that were analyzed included: age, education, income, marital status, race/ethnicity, smoking, diabetes, infrequent dental visits, and obesity (Carranza, Newman, Takei, & Klokkevold, 2006, p. 90-91; Nishida et al., 2000; Suvan et al., 2011). The variables were coded as follows: age, for oral contraceptive use 1=30-39 years; 2=40-49 years, for HRT 1=50-54 years; 2=55-59 years; 3=60-65 years, education 1=Less than high school education; 2=High school graduate; 3=Some college or above education, income 1= less than $25, 000; 2=$25, 000 to $54, 999; 3= More than $54, 999, marital status, for oral contraceptives, 1=Married; 2=Single; 3=Other (Widowed, divorced, separated and living with partner), for HRT, 1=Married; 2=Others (Single, widowed, divorced, separated and living with partner), race/ethnicity 1=Non-Hispanic White; 2=Non-Hispanic Black; 3=Hispanic; 4=Others, smoking 1=Smoking everyday/somedays; 2=Not at all; 3=Missing, diabetes 1=Diabetic and borderline diabetes; 2= No diabetes, infrequent dental visits 1=Less than 1 year ago; 2=More than 1 year ago and never have been, and, obesity 1= BMI 0-25 Kg/m^2; 2=25-30 Kg/m^2; 3= >30 Kg/m^2.

4.5. Data Analysis

SAS-callable SUDAAN was used for univariate, bivariate and multivariate analyses to account for the complex sampling design used by NHANES.

4.5.1 Univariate Analysis

Frequencies and percentages were used to describe the study population.

4.5.2. Bivariate Analysis

Unadjusted odds ratios and 95% confidence intervals were calculated using logistic regression to examine the crude association between the use of oral contraceptives and periodontitis (Table 2) as well as the crude association between the use of hormone replacement therapy and periodontitis (Table 3). In addition, other factors associated with periodontitis were identified.

4.5.3. Multivariate Analysis

Adjusted odds ratio and 95% confidence intervals were calculated using multivariate logistic regression to determine the association between the exposure-disease associations while controlling for confounding (Table 4). Factors to be adjusted in the final model were added to the model one at a time. If the magnitude of the odds ratio changed by 10% or more upon addition of a covariate, the variable was considered a confounder of the exposure-disease association (Maldonado and Greenland, 1993).

4.6. Power and Sample Size

A total of 606 women were available for the oral contraceptive-periodontitis analysis. Setting alpha at 0.05, power at 80%, the ratio of unexposed (never used oral contraceptives) to exposed (history of oral contraceptive use) at 0.26:1, and the prevalence of periodontal diseases among the unexposed at 4.29%, the smallest detectable OR is approximately 2.82.

A total of 505 women were available for the HRT-periodontitis analysis. Considering women who have not used hormone replacement therapy as the unexposed population, the ratio of unexposed to exposed is 3.04:1. Setting alpha at 0.05, power at

80%, and the prevalence of periodontal diseases among the unexposed at 24.75%, the

smallest detectable OR is approximately 5.88.

CHAPTER 5: RESULTS

5.1. Univariate Analysis

5.1.1. Oral Contraceptives

A total of 4900 women participated in NHANES. Of these women, 3419 completed the reproductive health questionnaire and underwent an oral exam. For the oral contraceptives-periodontitis analysis women who were not 30-49 years old were excluded (n=3324). Additionally, women for whom the attachment loss could not be assessed were excluded from the study (n=347). Thus, 606 women were available for the analysis.

For the HRT-periodontitis analysis, 3419 women who completed the reproductive health questionnaire and underwent an oral exam were considered for the analysis. Women who were not between the ages of 50-65 years were excluded (n=2621). Furthermore, women for whom the attachment loss could not be assessed were excluded (n=293). Thus, 505 women remained for analysis.

The oral contraceptives-periodontitis analysis consisted of 623 women 30-49 years old. Among women who had ever used OCs, 11.23% had evidence of periodontitis (Table 1). In contrast, 21.05% of non-oral contraceptive users had periodontitis. Oral contraceptive users were fairly distributed between the age groups (30-39 years: 46.18% and 40-49 years: 53.82%). In comparison, among the non-oral contraceptive users, the 30-39 age group included more women as compared to the 40-49 years age group

(57.10% and 42.90%, respectively). Among oral contraceptive users, the largest

proportion were Non-Hispanic White (68.92%) followed by Non-Hispanic Black Women

(11.88%), Hispanic (13.73%) and "other" races (5.47%). Among the non-oral

contraceptive users, 32.98% of women were Non-Hispanic White, 16.17% were Non-

Hispanic Black, 28.97% were Hispanics and 21.88% belonged to the "other" category.

The prevalence of obesity was similar among the oral contraceptive use and non-oral

contraceptive use groups (39.74% and 38.12%, respectively). Among the oral

contraceptive users, more than three-fourths of women had some college or higher level

of education, 13.65% of women had high school education and 11.00% had less than

high school education. In contrast, 58.43% of non-oral contraceptive user women had

some college or higher level of education, 22.40% women had a high school education,

and 19.17% of women had less than high school education.

5.1.2. Hormonal Replacement Therapy

Among the HRT users, 15.41% had evidence of periodontitis while 20.93% of

non-HRT users showed evidence of the disease (Table 2). Among the HRT users, 50% of

the women who used HRT were 60-65 years old, 27.68% were 55-59 years old and

22.26% were 50-54 years old. In comparison, non-HRT using women were more evenly

distributed: 39.76% women were 50-54 years old, 33.06% were 55-59 years old and

27.17% were 60-65 years old. Among the HRT users, 85.73% of women were non-

Hispanic White, 5.25% were Non-Hispanic Black women (5.25%), 5.64% were Hispanic,

and 3.39% belonged to the 'other' category. The distribution among non-HRT users was

as follows: 67.97% Non-Hispanic White, 13.93% Non-Hispanic Black, 10.14% Hispanic

and 7.96% "other." A majority of women in the HRT users group (34.98%) and non-

HRT users group were overweight/obese (40.79%). Among the HRT users, the majority of women had some college education or above (86.10%) while 10.99% had a high school education and 3.39% had less than a high school education. Among the non-HRT users, a somewhat similar distribution was seen with the majority of women having some college or higher level of education (62.45%), 23.41% of women having a high school level education, and 14.14% of women having less than a high school education.

5.2. Bivariate Analysis

5.2.1. Oral Contraceptives

In the unadjusted model, women who used OCs had decreased odds of periodontitis and this result was statistically significant (OR=0.47; 95% CI: 0.23-0.97; Table 3). Women between the ages of 40 to 49 years had over twice the odds of periodontitis, as compared to women who were 30-39 years old and this result was statistically significant (CI: 1.22-4.35). Compared to Non-Hispanic White women, Non-Hispanic Black women had nearly three times the odds of periodontitis (OR=2.96; 95% CI: 1.19-7.36) and Hispanic women had twice the odds of periodontitis (OR=2.04; 95% CI: 1.08-3.86) and these results were statistically significant. While women of other races also had increased odds of periodontitis, this result was not statistically significant (OR=1.56; 95% CI: 0.34-7.14). When comparing income (≥$54, 999 as referent), women with household income levels $25, 000 - $49, 999, had more than 7 times the odds of periodontitis (OR=7.37; 95% CI=2.72-19.97) and women with household income levels less than $25, 000 had 11 times the odds of periodontitis (OR=11.12; 95% CI: 4.56-27.11) and these results were statistically significant. Compared to women who visited a dentist within the last year, women who had not been to a dentist for more than one year

had increased odds of periodontitis and this result was statistically significant (OR=3.14; 95% CI: 1.39-7.09). Women with less than a high school graduate degree and women with a high school diploma had nearly four times the odds of periodontitis as compared to women who had at least some college education (OR=3.93; 95% CI: 1.65-9.38 and OR=3.72; 95% CI: 1.91-7.23, respectively).

5.2.2. Hormonal Replacement Therapy

In the unadjusted model, women who used HRT had decreased odds of periodontitis as compared to women who were HRT users, however, this finding was not statistically significant (OR=0.69; CI: 0.33-1.44; Table 4). As compared to women who were married, women who were in the "other" category (i.e. single, divorced, living with partner or widowed) had over twice the odds of periodontitis, and this result was statistically significant (OR=2.43; CI: 1.66-3.56). Women who were smokers had higher odds of periodontitis as compared to women who were non-smokers and this result was statistically significant (OR=4.81; CI: 1.55-14.89). Women with household income levels < $54,999, had nearly three times the odds of periodontitis as compared to women with an income level ≥$54,999 ($25,000: OR=2.68; 95% CI: 1.22-5.92 and $25,000-$54,999: OR=2.70; 95% CI:1.19-6.15 respectively). Women who had been to a dentist more than one year ago had almost three times the odds of periodontitis (OR=3.12; CI: 2.01-4.86) as compared to women who visited a dentist within the past year and this result was statistically significant. Women with less than a high school education had nearly five times the odds of periodontitis (OR=4.56; CI: 2.31-9.01) and women with a high school education had nearly twice the odds of periodontitis (OR=1.87; CI: 1.12-3.13) as compared to women who had some college education or higher.

5.3. Multivariate Analysis

5.3.1. Oral Contraceptives

After adjusting for age, race, income, education and alcohol use, the association between OCs use and periodontitis was attenuated and no longer significant. Specifically, women who had ever used OCs had 0.74 times the odds of periodontitis as compared to females who had never used OCs (95% CI: 0.36-1.50; Table 5).

5.3.2. Hormonal Replacement Therapy

After adjusting for race, income, education, last dental visit, smoking, and marital status, the HRT-periodontitis association reversed direction and remained not statistically significant. Specifically, women who had used HRT had a 17% increased odds of periodontitis as compared to women who had never used HRT (95% CI: 0.55-2.49; Table 5).

CHAPTER 6: DISCUSSION

6.1. Summary of Findings

The current study found that women who ever took oral contraceptives had decreased odds of periodontitis as compared to women who never took oral contraceptives and this result was statistically significant. After adjusting for age, race/ethnicity, income, education and alcohol use, the association was attenuated and no longer statistically significant. The current study also found that women who ever were on HRT had decreased odds of periodontitis as compared to women who were never on HRT, however, this result was not statistically significant. After adjusting for race/ethnicity, income, education, last dental visit, smoking and marital status, the association reversed in direction and remained not statistically significant.

6.2. Consistency with Previous Research

A study conducted by Haerlan-Adrakani et al in 2010 found no association between the use of oral contraceptives and loss of attachment among women who were oral contraceptive users. After adjustment, the results of the current study were attenuated and no longer statistically significant. Although the study by Haerlan-Adrakani et al. was conducted in Iran and had a smaller sample size (n=70 for the Haerlan-Adrakani study compared to the n=606 for the current study), results were somewhat consistent with this study.

Taichman et al. in 2005 conducted a secondary data analysis on NHANES I and NHANES III data and found associations in the same direction as this study (NHANES I: OR=0.36, 95% CI: 0.13-0.96 and NHANES III: OR=0.73, CI: 0.5-1.07). In fact, the odds ratio for the NHANES III analysis was nearly identical to the odds ratio observed in the current study, and both were not statistically significant. The findings for NHANES I may have differed from findings for NHANES III and the current study due to differences in measuring periodontitis. Periodontitis in NHANES I was measured by periodontal index which is less objective than attachment loss which was used in NHANES III and the current study.

A cross-sectional study by Mullaly et al. in 2007, was conducted in the United Kingdom in 2007 and found a harmful association between current oral contraceptive use and attachment loss (2.6 mm versus 1.7 mm, p=0.017). The findings of this study were inconsistent with the study by Mullaly et al. One reason for this discrepancy may be because the participants for the study in the United Kingdom were recruited from a general dental practice and they may have already had evidence of periodontitis. Differences between the United Kingdom and the United States may also account for the inconsistent findings.

For the association between HRT and periodontitis, there was only one study conducted in the past 10 years by Marcos et al., in Spain in 2005. This study measured periodontitis by using probing depths. The study by Marcos et al. found a protective association between the use of HRT and periodontitis, however the results of the current study found a positive, although not statistically significant, association after adjusting

for confounders. The study by Marcos et al. was conducted in Spain and had a smaller sample size which may explain the apparent inconsistency in findings.

6.3. Strengths and Limitations

6.3.1. Non-differential Misclassification

Non-differential misclassification may have occurred for the exposures and the outcome. The exposures, oral contraceptive use and use of hormonal replacement therapy, were measured based on self-report. It is possible that participants may have had difficulty in remembering the use of oral contraceptives and HRT. Any non-differential misclassification of the exposures would likely bias the results towards the null.

Non-differential misclassification of the outcome is less likely. The periodontal exam was conducted by trained and calibrated examiners. While this training limits misclassification, it is possible that non-differential misclassification might have occurred due to human error. If such errors occurred it would likely bias the association towards the null.

6.3.2. Selection Bias

A complex sampling method is used in NHANES to select participants for the survey (Johnson, Dohrmann, Burt and Mohadjer, 2014). The average overall response rate for the interviewed females included in the study was approximately 72.6% and 69.4% for those completing the physical exam and laboratory components, respectively (CDC, 2013). These response rates are much higher than other national surveys such as the Behavioral Risk Factor Surveillance System (BRFSS). Response rates for the 2012 BRFSS were 49.6% for landline and 37.8% for cell phone (CDC, 2014). Thus, selection bias is unlikely to have occurred. However, it is possible that females who participated in

the study differed from those who did not participate. For example, females who participated may have had better knowledge about hormonal regimens and oral health as compared to those women who did not participate.

6.3.3. Information Bias

Information bias is unlikely to have occurred in this study since trained interviewers helped to administer the reproductive health section of the survey in the MECs and other trained dental professionals conducted the dental exams at another time. Thus, it is unlikely that a woman's self-report of oral contraceptive or HRT use influenced the dental professional conducting her exam. However, a possibility exists that women who have periodontal diseases may be more aware of past behaviors, including the use oral contraceptives or HRT.

6.3.4. Confounding

The confounders that were assessed in the study were restricted to the variables available in the NHANES data. This study considered multiple potential confounders including age, race/ethnicity, smoking, marital status, alcohol use, BMI, income, dental visits, and education. Research has shown an association between reduced dietary intake of calcium and periodontitis, however, calcium information was not available in the NHANES dataset (Nishida et al., 2000). Thus, failure to control for this confounder could have resulted in an over- or under-estimate of the association. Failure to control for possible unknown confounders of the outcome-exposure association could have resulted in an over- or under-estimation of the true association.

6.3.5. Strengths

The current study had a number of strengths. It is the first study to examine the association between the use of modern oral contraceptives and periodontitis in a US population. The previous study conducted by Taichman et al. was also on NHANES datasets (specifically, NHANES I and NHANES III), however, the composition of oral contraceptives was different when NHANES I and NHANES III were conducted. This study differed from some previous studies with respect to how the outcome was measured. This study used attachment loss which is the most objective measure for periodontitis. Other studies have used pocket depth and periodontal index which are less objective ways to measure periodontitis. In addition, this study is the first study to examine an association between HRT and periodontitis in a nationally representative sample of US women.

6.3.6. Generalizability

The 2011-2012 NHANES utilized a complex, four stage design to fully capture a representative sample of the US population and oversampled underrepresented populations for accuracy (Johnson, Dohrmann, Burt and Mohadjer, 2014). Thus, the results of this study are likely generalizable to US women who are 30 years and older.

6.4. Significance and Implications

Research has shown that periodontal disease may influence numerous chronic diseases including diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, and acute bacterial pneumonia (Carranza, 2002, p.230). Given that more than 80% of US women have used oral contraceptives at some point during their lives (CDC, 2010) and approximately 5% of women use HRT (Sprague et al., 2012), it is important to

determine if there is an association between these hormonal regimens and periodontal disease since periodontitis can lead to serious consequences if left untreated.

Despite the fact that this study did not find statistically significant associations between hormonal regimens and periodontitis, dentists and other medical professionals should continue to inquire about oral contraceptive use and hormonal replacement therapy use when treating patients since there are gum diseases other than periodontitis for which these exposures could be important. Due to the possibility that HRT use may increase the odds of periodontitis, dentists should take extra care with women who use or have used HRT and reinforce the importance of oral hygiene. Although the use of oral contraceptives appeared to be a protective factor in the development of periodontitis, women should continue to be educated on the importance of maintaining proper oral hygiene since the protection afforded could be due to the hormonal composition of oral contraceptives which has changed over the decades.

Findings related to the association between oral contraceptives and HRT with periodontitis have been inconsistent, thus more research is needed. Future studies should consider the duration of oral contraceptive use rather than just ever use of OCs and HRT. A longitudinal cohort may also be desirable so the true sequence of events can be better understood and so the duration of oral contraceptive and HRT use can be measured better. Determining the relationship between the use of these hormonal regimens and periodontitis could guide dentists in taking better care of women on these regimens and tailoring case-specific treatment plans.

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Table 1: Study sample characteristics of women who participated in NHANES according to use of oral contraceptive, 2011-2012

Outcome and demographic variables	OC user N=479 (79.04%)	Non-OC user N=127 (20.96%)
Periodontitis		
Yes	68[11.23]	26[21.05]
No	411[88.77]	101[78.95]
Age		
30-39	242[46.18]	68[57.10]
40-49	237[53.82]	59[42.90]
Marital status		
Married	278[64.15]	69[52.90]
Single	81[11.51]	23[16.19]
Other	120[24.34]	35[30.92]
Smoking		
Yes	86[17.21]	21[21.47]
No	83[22.32]	14[13.74]
Missing	310[60.47]	92[64.79]
Alcohol use		
Yes	352[79.35]	64[52.90]
No	127[20.65]	63[47.10]
Race/ethnicity		
Non-Hispanic White	218[68.92]	21[32.98]
	112[11.88]	25[16.17]
Non-Hispanic Black	93[13.73]	33[28.97]
Hispanic	56[05.47]	48[21.88]
Other		

Household income		
<25,000	114[15.93]	40[31.06]
25,000-54,999	134[25.68]	36[31.62]
≥54,999	231[58.40]	51[37.33]
BMI		
Underweight (<25)	131[30.23]	47[28.01]
Normal (25-30)	136[30.03]	36[33.87]
Overweight/Obese (>30)	212[39.74]	44[38.12]
Last dental visit		
≤ 1 year ago	284[64.10]	81[62.78]
>1 year ago and never have been	195[35.90]	46[37.22]

Table 1: (continued)

Education		
Less than High School	68[11.00]	27[19.17]
	66[13.65]	22[22.40]
High School Graduate	345[75.35]	78[58.43]
Some college or above		
Diabetes		
Yes	33[06.28]	9[05.78]
No	446[93.72]	118[94.22]

Table 2: Study sample characteristics of women who participated in NHANES according to use of hormonal replacement therapy, 2011-2012

Outcome and demographic variables	HRT user N=125 (24.75%)	Non-HRT user N=380 (75.25)
Periodontitis		
Yes	27[15.41]	125[20.93]
No	98[84.57]	255[79.07]
Age		
50-54	23[22.26]	151[39.76]
55-59	29[27.68]	103[33.06]
60-65	73[50.06]	126[27.17]
Marital status		
Married	72[66.77]	166[52.96]
Other	53[33.23]	214[47.04]
Smoking		
Yes	14[14.88]	51[10.61]
No	30[31.48]	80[27.14]
Missing	81[53.64]	249[62.25]
Alcohol use		
Yes	87[84.56]	220[71.17]
No	38[15.44]	160[28.83]
Race/ethnicity		
Non-Hispanic White	57[85.73]	109[67.97]
	31[5.25]	134[13.93]

Non-Hispanic Black	28[05.64]	78[10.14]
Hispanic	9[03.39]	59[07.96]
Other		
Household income		
<25,000	28[11.78]	132[24.75]
25,000-54,999	30[25.9]	117[26.95]
≥54,999	67[62.83]	131[48.30]
BMI		
Underweight (<25)	23[21.05]	90[25.69]
Normal (25-30)	50[43.97]	109[33.52]
Overweight/Obese (>30)	52[34.98]	181[40.79]

Table 2: (continued)

Last dental visit		
≤ 1 year ago	95[85.70]	222[63.00]
>1 year ago and never have been	30[14.30]	158[37.00]
Education		
Less than High School	13[2.91]	85[14.14]
High School Graduate	20[10.99]	92[23.41]
Some college or above	92[86.10]	203[62.45]
Diabetes		
Yes	20[11.88]	89[18.52]
No	105[88.12]	291[81.48]

Table 3: Unadjusted odds ratios (OR) and 95% Confidence Intervals (CI) of oral contraceptive use, other risk factors and periodontitis; 2011-2012 NHANES

	Periodontitis	
Exposure and demographic variables	**OR**	**95% CI**
Use of oral contraceptives		
Yes	0.47	0.23-0.97
No	1.00	Referent
Age		
30-39	1.00	Referent
40-49	2.30	1.22-4.35
Marital status		
Married	1.00	Referent
Single	2.38	1.35-4.21
Other	2.21	0.95-5.13
Smoking		
Yes	3.45	1.32-9.03
No	1.00	Referent
Missing	0.71	0.34-1.45
Alcohol use		
Yes	0.58	0.3-1.12
No	1.00	Referent
Race/ethnicity		

Non-Hispanic White	1.00	Referent
	2.96	1.19-7.36
Non-Hispanic Black	2.04	1.08-3.86
Hispanic	1.56	0.34-7.14
Other		
Household income		
<$25,000	11.12	4.56-27.11
$25,000-$54,999	7.37	2.72-19.97
≥$54,999	1.00	Referent
BMI		
Underweight (<25)	0.58	0.29-1.16
Normal (25-30)	1.00	Referent
Overweight/Obese (>30)	1.55	0.77-3.13

Table 3: (continued)

Last Dental visit		
≤ 1 year ago	1.00	Referent
>1 year ago and never have been	3.13	1.4-7
Education		
Less than High School	3.93	1.65-9.38
	3.72	1.91-7.23
High School Graduate	1.00	Referent
Some college or above		
Diabetes		
Yes	1.3	0.44-3.86
No	1.00	Referent

Table 4: Unadjusted odds ratios (OR) and 95% Confidence Intervals (CI) of hormone replacement therapy use, other factors and periodontitis; 2011-2012 NHANES

	Periodontitis	
Exposure and demographic variables	OR	95% CI
Use of HRT		
Yes	0.69	0.33-1.44
No	1.00	Referent
Age		
50-54	1.00	Referent
55-59	0.97	0.39-2.47
60-65	0.63	0.32-1.21
Marital status		
Married	1.00	Referent
Other	2.43	1.66-3.56
Smoking		
Yes	4.81	1.55-14.89
No	1.00	Referent
Missing	1.23	0.52-2.91
Alcohol use		
Yes	0.66	0.33-1.32
No	1.00	Referent

Race/ethnicity

Non-Hispanic White	1.00	Referent
	3.89	1.75-8.66
Non-Hispanic Black	3.47	1.4-8.55
Hispanic	1.32	0.6-2.9
Other		

Household income

	2.68	1.22-5.92
<$25,000	2.7	1.19-6.15
$25,000-$54,999	1.00	Referent
≥$54,999		

Table 4: (continued)

BMI		
Underweight (<25)	1.25	0.48-3.31
Normal (25-30)	1.00	Referent
Overweight/Obese (>30)	0.84	0.49-1.45
Last Dental visit		
≤ 1 year ago	1.00	Referent
>1 year ago and never have been	3.12	2.01-4.86
Education		
Less than High School	4.56	2.31-9.01
High School Graduate	1.87	1.12-3.13
Some college or above	1.00	Referent
Diabetes		
Yes	1.02	0.66-1.57
No	1.00	Referent

Table 5: Adjusted odds ratio of use of hormonal regimens and periodontitis; NHANES 2011-2012

Exposure	Periodontitis	
	OR	**95% CI**
Use of oral contraceptives		
Yes	0.74	0.36-1.50
No	1.00	Referent
Use of hormonal replacement therapy		
Yes	1.17	0.55-2.49
No	1.00	Referent