T.C.
YEDITEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PERIODONTOLOGY

# EVALUATION OF THE ASSOCIATION BETWEEN PERIODONTAL STATUS AND INFERTILITY PARAMETERS IN WOMEN UNDERGOING IN VITRO FERTILIZATION TREATMENT: A CROSS-SECTIONAL CLINICAL STUDY

DOCTOR OF PHILOSOPHY THESIS

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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..... and numbered .....

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## DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

16/12/2022

Naz KURT

**DEDICATION**

To my mother *Zeynep*, who is always there for me with her support and love, who made it easier for me to write this thesis by lightening my burden,

To my father *Ayberk,* who is a light and an example to me with his support and love for his family, respect for his job, academic success, and hard work,

To my brother *Ata,* whom I can't imagine a life without,

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| | |
|---|---|
| AAP | American Association of Periodontology |
| AFC | Antral Follicle Count |
| AMH | Anti-Müllerian Hormone |
| BMI | Body Mass Index |
| BOP | Bleeding on Probing |
| CAL | Clinical Attachment Level |
| CEJ | Cemento-enamel Junction |
| CI | Confidence Interval |
| CRP | C-reactive protein |
| E2 | Estradiol |
| EFP | European Federation of Periodontology |
| FSH | Follicle Stimulating Hormone |
| GI | Gingival Index |
| GStIGrB | Generalized Stage I Grade B |
| GStIIGrB | Generalized Stage II Grade B |
| ICC | Intra-class Correlation |
| IVF | In Vitro Fertilization |
| JE | Junctional Epithelium |
| kg/m2 | kilogram/ meters squared |
| LH | Luteinizing Hormone |
| LStIGrB | Localized Stage I Grade B |
| mIU/ L | milli-international units per liter |
| mm | millimeter |
| ng/ mL | nanograms per milliliter |
| OHIP | Oral Health Impact Profile |
| OHRQoL | Oral Health-related Quality of Life |
| PCOS | Polycystic Ovary Syndrome |
| PD | Periodontal Disease |
| pg/mL | picograms per milliliter |
| PI | Plaque Index |

| | |
|---|---|
| PPD | Probing Pocket Depth |
| QoL | Quality of Life |
| RBL | Radiographic Bone Loss |
| SD | Standard Deviation |
| SPSS | Statistical Packages of Social Sciences |
| TSH | Thyroid Stimulating Hormone |
| WHO | World Health Organization |

## ABSTRACT

**Kurt, N. (2022). Evaluation of the Association Between Periodontal Status and Infertility Parameters in Women Undergoing In Vitro Fertilization Treatment: A Cross-Sectional Clinical Study, Yeditepe University, Institute of Health Sciences, Department of Periodontology, PhD thesis, Istanbul.**

The aim of this thesis was to examine infertility and periodontal parameters, and periodontal disease status in women attending in vitro fertilization (IVF) clinics. The hypothesis is that plaque-induced periodontal diseases are possible impact factors in infertility. The other purpose of this thesis was to evaluate age, educational level, body mass index, smoking habits, oral hygiene-related behaviors, and oral health-related quality of life (OHRQoL) in infertile females attending IVF clinics. After the gynecological examination and blood tests, infertile female patients were referred to the Yeditepe University, Faculty of Dentistry, Department of Periodontology. Data of age, educational level, body mass index, smoking habits, oral hygiene-related behaviors, and OHRQoL were collected from patients. Thereafter, periodontal parameters (plaque index, probing pocket depth, clinical attachment level, bleeding on probing) were recorded. Recruited patients were classified into periodontal disease status groups. These groups were compared for infertility parameters as follicle-stimulating hormone (FSH), estradiol (E2), anti-Müllerian hormone (AMH), and antral follicle count (AFC). Correlations between periodontal and infertility parameters were assessed. The results showed that all infertile women in the study population presented plaque-induced periodontal diseases. Both AMH levels and AFC values were significantly lower in the generalized Stage II Grade B periodontitis group compared to the gingivitis group. Regarding the whole study population, FSH was significantly and positively correlated with all periodontal parameters. AMH was significantly and negatively correlated with all periodontal parameters except clinical attachment level. AFC was significantly and negatively correlated with all periodontal parameters. Within the limitations of this study, present findings encourage that a larger study population should further be undertaken to confirm the impact of periodontal diseases on infertility and to determine the effect of pre-existing periodontal disease on IVF treatment, achievement of pregnancy as well as birth outcomes.



**Keywords:** gingivitis, infertility, in vitro fertilization, periodontal disease, periodontitis

## ABSTRACT (Turkish)

**Kurt, N. (2022). İn Vitro Fertilizasyon Tedavisi Gören Hastalarda Periodontal Durum ve İnfertilite Parametreleri Arasındaki İlişkinin Değerlendirilmesi: Kesitsel Bir Çalışma, Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Periodontoloji Anabilim Dalı, Doktora Tezi, İstanbul.**

Bu tezin amacı, in vitro fertilizasyon (IVF) kliniklerine başvuran kadınlarda infertilite parametreleri ile periodontal parametreleri ve periodontal hastalık durumunu incelemektir. Hipotez, plak kaynaklı periodontal hastalığın infertilite için olası etki faktörü olmasıdır. Tezin diğer amacı, IVF kliniklerine başvuran infertil kadınlarda yaş, eğitim düzeyi, vücut kitle indeksi, sigara içme alışkanlıkları, ağız hijyeni ile ilgili davranışlar ve ağız sağlığı ile ilişkili yaşam kalitesini değerlendirmektir. İnfertil kadın hastalar, jinekolojik muayene ve kan tahlillerinin ardından Yeditepe Üniversitesi Diş Hekimliği Fakültesi Periodontoloji Anabilim Dalı'na yönlendirilmiştir. Hastalardan yaş, eğitim düzeyi, vücut kitle indeksi, sigara içme alışkanlıkları, ağız hijyeni ile ilgili davranışlar ve ağız sağlığı ile ilişkili yaşam kalitesi verileri toplanmıştır. Daha sonra periodontal parametreler (plak indeksi, cep derinliği, klinik ataşman seviyesi, sondalamada kanama) kaydedilmiştir. Hastalar periodontal hastalık durumlarına göre sınıflandırılmıştır. Bu gruplar folikül uyarıcı hormon (FSH), estradiol (E2), anti-Müllerian hormon (AMH) ve antral folikül sayısı (AFC) gibi infertilite parametreleri açısından karşılaştırılmıştır. Periodontal ve infertilite parametreleri arasındaki korelasyonlar değerlendirilmiştir. Bu çalışmanın sonuçları, çalışma populasyonundaki tüm infertil kadınların plak kaynaklı periodontal hastalığa sahip olduğunu göstermiştir. Generalize Evre II Derece B periodontitis grubunda AMH seviyeleri ve AFC değerleri, gingivitis grubuna kıyasla anlamlı derecede düşük bulunmuştur. Tüm çalışma popülasyonu göz önüne alındığında, FSH ile tüm periodontal parametreler arasında anlamlı ve pozitif bir korelasyon olduğu görülmüştür. AMH, klinik ataşman seviyesi dışındaki tüm periodontal parametrelerle anlamlı ve negatif korelasyon göstermiştir. AFC, tüm periodontal parametrelerle anlamlı ve negatif korelasyon göstermiştir. Çalışmanın limitasyonları dahilinde, mevcut bulgular, periodontal hastalığın IVF tedavisi, gebelik başarısı ve doğum sonuçları üzerindeki etkisini de belirlemek için daha geniş çalışma popülasyonunda çalışılmasını teşvik eder niteliktedir.

**Anahtar Kelimeler:** gingivitis, infertilite, in vitro fertilizasyon, periodontal hastalık, periodontitis

# 1. INTRODUCTION AND PURPOSE

Periodontal disease (PD)s are multifactorial, chronic, inflammatory diseases of the oral cavity (1). The main etiological factor of PD is microbial dental plaque biofilm, besides its interaction with the host response (2). Biofilm accumulation leads to the development of gingival inflammation (2, 3). This inflammation is gingivitis, a reversible inflammatory disease. When gingivitis progresses, the condition turns into periodontitis (3). Periodontitis is an irreversible inflammatory disease characterized by the progressive destruction of the periodontium resulting from the imbalance between the dysbiotic biofilm and the host's immune-inflammatory response (4). Quality of life (QoL) is significantly affected by PDs (5).

It has been reported that periodontal infections do not only affect the periodontium but also affect and associate with various systemic diseases and conditions (2, 6) such as the increased risk of adverse pregnancy outcomes (e.g., preterm labor, low birth weight babies, pre-eclampsia and miscarriage) (6), besides many others. More recently, a relationship has been found between PDs and infertility (7-23).

Infertility is the inability of a couple to conceive after one year or more of unprotected regular sexual intercourse (24). In vitro fertilization (IVF) is one of the most common treatment approaches to overcome infertility and achieve conception (10). Serum endocrine markers such as follicle-stimulating hormone (FSH), estradiol (E2), anti-Müllerian hormone (AMH) levels, and ultrasound-based antral follicle count (AFC) indicate ovarian reserve, predict IVF success and pregnancy outcome (25). Therefore, an accurate assessment of these parameters, before the patient enters an IVF program, is crucial (25).

A number of studies with different materials and methods reported a relationship between female infertility and the PD status of infertile women. Studies have hypothesized that PDs may act as a modifiable risk factor limiting conception, and reduce female fertility (9, 10, 12, 15, 20, 22, 23). On the other hand, the link between reproductive failure and vaginal infections has been demonstrated due to increased plasma cytokine levels and increased immunity to heat shock proteins (26, 27). Furthermore, many of the gynecological studies provided evidence for increased

immunity in the presence of clinical infections (28) that were associated with IVF failures (29, 30). Based on these evidences, another periodontal study investigating specifically ovulation induction's effect on gingival inflammation during the treatment of infertility stated that PDs can both affect reproduction and the outcome of IVF since they are chronic infections that may lead to bacteremia, endotoxemia, increased plasma levels of cytokines and prostoglandins and increased immunity to heat shock proteins (31).

As the first study to investigate the relationship between conception and PDs, Hart et al. declared that periodontitis incidence increases the time to conception in non-Caucasian women (9). Pavlatou et al. examined the relationship between periodontal status and IVF outcome parameters before and after IVF treatment and concluded that poor periodontal status is associated with poor IVF outcome parameters (10). Lalasa et al. revealed that infertile women had significantly higher clinical attachment loss compared to fertile women (13).

Therefore, periodontal examination and treatment may be of critical importance for women seeking for IVF treatment and pregnancy. Comprehensive studies are needed to understand the link between PDs and infertility.

To the best of our knowledge, there is no research in the literature investigating the relationship between infertility parameters (FSH, E2, AMH and AFC) and the PD status of infertile women attending IVF treatment. The aims of this thesis are firstly to examine age, educational level, body mass index (BMI), smoking habits, oral hygiene-related behaviors, and oral health-related quality of life (OHRQoL) and thereafter, to find out whether a relationship exists between PD status (PD classification), periodontal parameters (clinical measurements) and infertility parameters in infertile women before IVF treatment. The hypothesis is that the plaque-induced PDs are possible impact factors in infertility.

# 2. LITERATURE REVIEW

## 2.1. Healthy Periodontium

The periodontium is a biological unit that attaches teeth to the maxillary and mandibular bones and provides support for the teeth to maintain their functions (32). It consists of gingiva, periodontal ligament, cementum, and alveolar bone. The gingiva, which is formed of free and attached gingiva, surrounds the cervical part of the teeth and conceals the alveolar bone (32). The attached gingiva continues from the cemento-enamel junction (CEJ) to the mucogingival junction. The free gingiva, which extends from gingival margin to the CEJ, is coral pink in color with a firm consistency and dull surface (33, 34). Under clinically periodontally healthy conditions, a gingival sulcus exists with less than or equal to 3 mm depth. No clinical signs of gingival inflammation such as erythema, edema, bleeding, or exudate exist in clinically healthy periodontium. Physiological alveolar bone levels range from 1.0 to 3.0 mm apical to the CEJ (27). The structure of a healthy periodontium is shown in Figure 2.1.

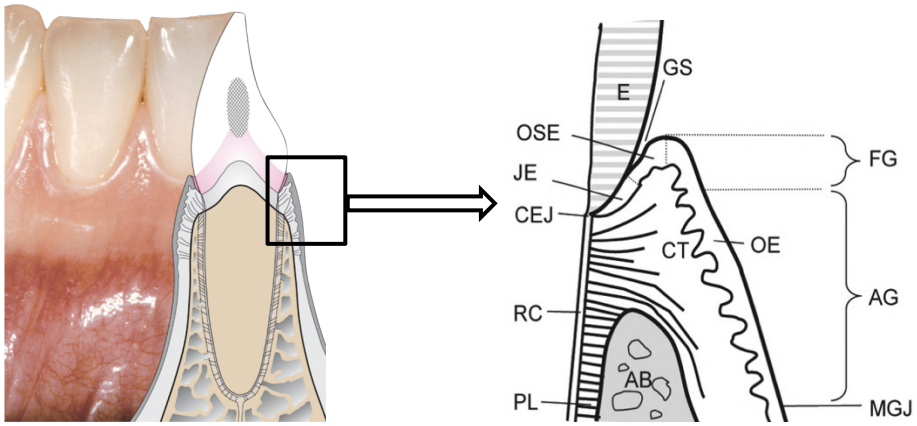


**Figure 2.1.** The structure of a healthy periodontium (35)

AB; alveolar bone, AG; attached gingiva, CEJ; cemento-enamel junction, CT; connective tissue, E; enamel, FG; free gingiva, GS; gingival sulcus, JE; junctional epithelium, MGJ; mucogingival junction, OE; oral epithelium, OSE; oral sulcular epithelium, PL; periodontal ligament, RC; root cementum

## 2.2. Periodontal Diseases

PDs are the most common chronic diseases in adults worldwide (36-39). PD initially presents as gingivitis, inflammation of the gingiva with erythema, edema, and bleeding (40). Biofilm-associated gingivitis is reversible when adequate oral hygiene is performed by the patient (41). In a susceptible host, gingivitis might evolve to periodontitis, resulting in periodontal attachment and alveolar bone loss (4, 40).

The main etiology of PD is the microbial dental plaque biofilm (2). In periodontal health, the microflora remains stable over time and in this level, host can control the biofilm by an inflammatory infiltrate as a part of biological immune surveillance (40, 42). A neutrophilic infiltrate is present even in periodontal health since bacteria are always present in the oral cavity (43). The nature of the relationship between the host and microorganisms is symbiotic in nature at this stage. Immune-inflammatory response of the host is proportionate and resolving (44).

However, if dental plaque biofilm accumulates without disruption, gingivitis develops due to a loss of symbiosis between the microbial dental plaque biofilm and the immune-inflammatory response of the host, and the development of incipient dysbiosis (45). Gram-negative, anaerobic or microaerophilic bacteria are associated with dysbiotic biofilm (46).

Gingival inflammation is a pre-requisite for periodontitis and progressive loss of attachment (47). In patients who are not susceptible, disease progression further than gingivitis does not take place, however, in susceptible patients an inappropriate and excessive host response may be triggered leading to periodontitis (42, 48).

In periodontitis, dysbiotic biofilm challenges the host and encounters a potent immune-inflammatory response (49). The host immune-inflammatory response can be overwhelmed by excessive biofilm accumulation, by host factors (e.g., interleukin-1 gene polymorphisms, immune disorders), by lifestyle factors (e.g., smoking, stress, diet) or by systemic diseases such as diabetes and, eventually, the host become susceptible to periodontitis (36, 50-52).

The destruction of the periodontium progresses in two ways (42, 53, 54). The first one is directly by periodontal pathogenic bacteria and their by-products, which destroy

the connective tissue and defense cells. The second one is by the inflammatory response triggered by the host, which leads to the gradual destruction of periodontium. Host's immune inflammatory cells release various inflammatory molecules, such as cytokines, prostaglandins, and matrix metalloproteinases. These inflammatory molecules cause the destruction of connective tissue and alveolar bone (42, 55, 56).

The classical model of PD pathogenesis was developed by Page and Kornman (1997) (53), however, with recent scientific findings this model has changed (42). The contemporary model of the pathogenesis of PDs is shown in Figure 2.2.

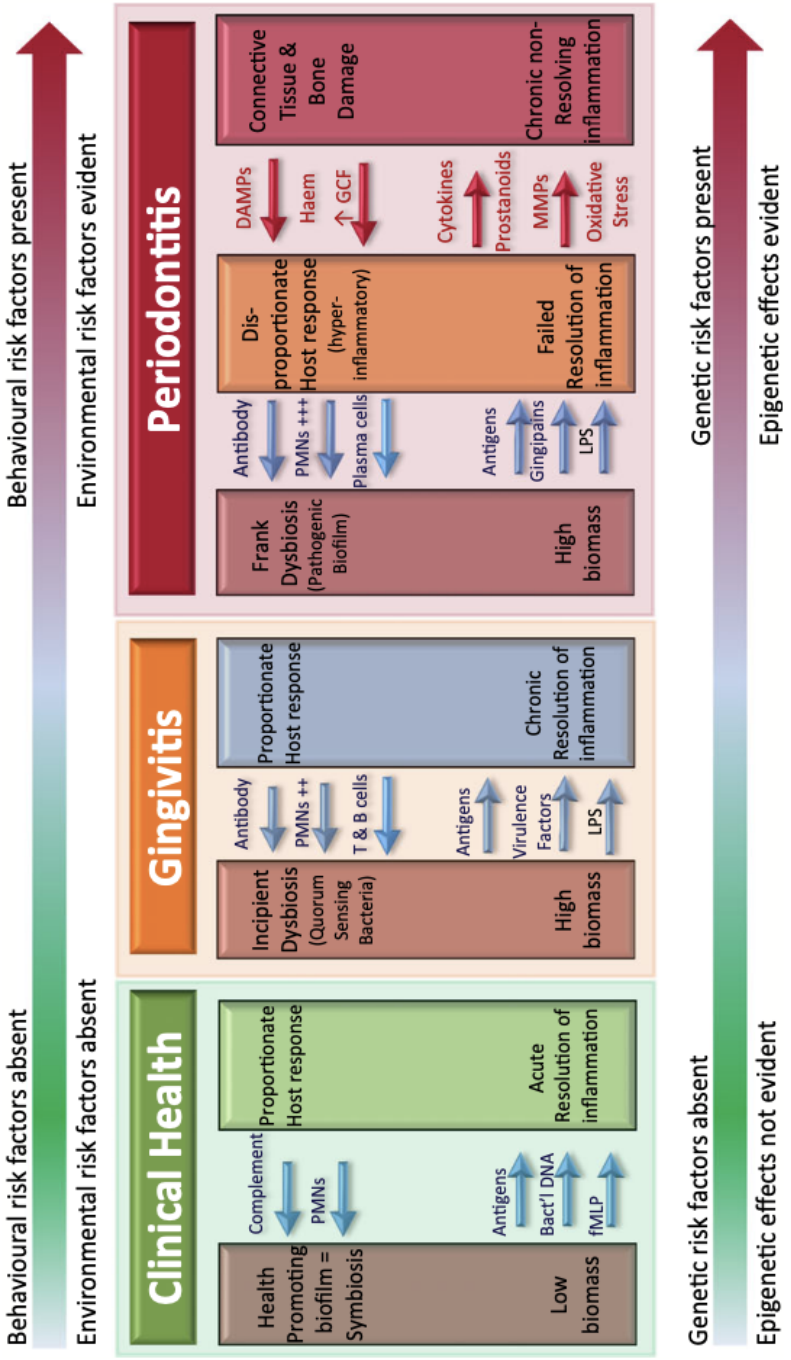


**Figure 2.2.** Contemporary model of the pathogenesis of periodontal diseases (42)

DAMPs; damage-associated molecular patterns, fMLP; N-formylmethionyl-leucyl-phenylalanine, GCF; gingival crevicular fluid, LPS; lipopolysaccharide, MMPs; matrix metalloproteinases, PMNs; polymorphonuclear neutrophils

## 2.3. Classification of Periodontal Diseases

The latest PD classification has been outlined and updated in the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions by the European Federation of Periodontology/American Association of Periodontology (EFP/AAP).

According to the EFP/AAP's classification in 2018, periodontal health is defined as an absence of clinically detectable inflammation (40). Clinically periodontally healthy patient exhibits less than 10% bleeding on probing (BOP) with no attachment and radiographic bone loss (RBL) attributed to periodontitis (40) (Figure 2.3).

Gingivitis on an intact periodontium (no attachment and bone loss) and gingivitis on a reduced periodontium in a patient without a history of periodontitis (e.g., in patients following crown lengthening surgery or with some form of gingival recession) is defined by the presence of gingival inflammation, exhibiting BOP at greater than or equal to 10% sites (3, 57) (Figure 2.3). A patient is diagnosed as localized gingivitis case if there are 10%–30% bleeding sites, whereas generalized gingivitis case if there are greater than 30% bleeding sites (3, 57).

| **Intact periodontium** | **Health** | **Gingivitis** |
|---|---|---|
| *Probing attachment loss* | No | No |
| *Probing pocket depths (assuming no pseudo pockets)* | ≤3 mm | ≤3 mm |
| *Bleeding on probing* | <10% | Yes (≥ 10%) |
| *Radiological bone loss* | No | No |
| Reduced periodontium<br>Non-periodontitis patient | **Health** | **Gingivitis** |
| *Probing attachment loss* | Yes | Yes |
| *Probing pocket depths (all sites & assuming no pseudo pockets)* | ≤3 mm | ≤3 mm |
| *Bleeding on probing* | <10% | Yes (≥ 10%) |
| *Radiological bone loss* | Possible | Possible |

**Figure 2.3.** Classification of periodontal health and gingivitis (57)

Periodontal support loss is assessed by RBL or interproximal clinical attachment loss or namely current level (CAL) (4, 48). A patient is a periodontitis case if there are detectable interdental CAL at ≥ 2 non-adjacent teeth; or buccal or oral CAL ≥ 3 mm with probing pocket depth > 3 mm detectable at ≥ 2 teeth (4). Periodontitis cases are further classified as staging and grading system (48).

Stage I to IV of periodontitis is dependent to the severity of the disease and the complexity of disease management (4, 48). Grade of periodontitis provides additional information about the anticipated treatment response, evidence of disease progression, assessment of the risk for rapid progression, and risk of possible impact of periodontitis on the patient's systemic health. Periodontitis grades A to C is assessed by evidence of direct or indirect rate of progression in three categories: slow, moderate, and rapid progression (4, 48) (Figure 2.4).

| | | Disease Severity and Complexity of Management | | | |
|---|---|---|---|---|---|
| | | Stage I: Initial periodontitis | Stage II: Moderate periodontitis | Stage III: Severe periodontitis with potential for additional tooth loss | Stage IV: Advanced periodontitis with extensive tooth loss and potential for loss of dentition |
| Evidence or risk of rapid progression, anticipated treatment response, and effects on systemic health | Grade A<br>Grade B<br>Grade C | **Individual Stage and Grade Assignment** | | | |

**Figure 2.4.** Framework for staging and grading of periodontitis (48)

Stage of periodontitis is defined as per interdental CAL at the site of the greatest loss of 1–2 mm as Stage I (mild periodontitis), 3–4 mm as Stage II (moderate periodontitis) and greater than or equal to 5 mm is considered as Stage III or Stage IV (severe periodontitis) (48). If available, the initial stage is determined with CAL, otherwise RBL should be used. Complexity factors may modify the stage, irrespective of CAL (48).

Staging further involves the extent and distribution of the disease in the dentition. If less than 30% of the teeth are involved, the extent of the disease is defined as localized, while if more than or equal to 30% of teeth are involved, it is defined as generalized (48) (Figure 2.5).

| Periodontitis stage | | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|---|
| Severity | Interdental CAL at site of greatest loss | 1–2 mm | 3–4 mm | ≥5 mm or extending to middle third of the root | ≥8 mm or extending to apical third of the root |
| | Radiographic bone loss | Coronal third (<15%) | Coronal third (15%–33%) | Extending to Middle third | Extending to Apical third |
| | Tooth loss | No Perio Tooth Loss | | Perio tooth loss ≤ 4 teeth | Perio tooth loss ≥ 5 teeth |
| Complexity | Local | Probing depth 3–4<br>Mostly horizontal bone loss | Probing depth 4–5<br>Mostly horizontal bone loss | In addition to Stage II Complexity<br>Probing depth ≥6<br>Vertical bone loss ≥3<br>Furcation II or III<br>Moderate ridge defect | In addition to Stage III Complexity<br>Need for complex rehabilitation due to:<br>Masticatory dysfunction<br>Secondary occlusal trauma (Tooth mobility ≥ 2)<br>Bite collapse, drifting, flaring<br>Less than 20 remaining teeth (10 opposing pairs)<br>Severe ridge defect |
| Extent & distribution | Add to Stage as descriptor | For each Stage, describe extent as localized (<30% of teeth involved), generalized or molar incisor pattern | | | |

**Figure 2.5.** Periodontitis stages (48)

When determining the grade of the periodontitis, if available, direct evidence of progression should be used, otherwise, indirect evidence of progression (RBL in the percentage of root length divided by the age of the patient) is used (48). Grade should initially be assumed as Grade B and the clinician should seek evidence to shift it towards grade A or C. Presence of risk factors, such as poorly controlled diabetes or smoking, may shift the grade to a higher level (48) (Figure 2.6).

Periodontitis may affect C-reactive protein (CRP) values, which indicate the patient's general systemic inflammation. For some patients, CRP values indicate an increased risk that periodontitis may be an inflammatory comorbidity. CRP levels and specific biomarkers may be added to the classification table if verified by specific evidence in the future (48) (Figure 2.6).

| Periodontitis grade | | | Grade A: Slow rate of progression | Grade B: Moderate rate of progression | Grade C: Rapid rate of progression |
|---|---|---|---|---|---|
| **Primary criteria** | Direct evidence of progression | Longitudinal data (radiographic bone loss or CAL) | Evidence of no loss over 5 years | <2 mm over 5 years | ≥2 mm over 5 years |
| | Indirect evidence of progression | % bone loss/age | <0.25 | 0.25 to 1.0 | >1.0 |
| | | Case phenotype | Heavy biofilm deposits with low levels of destruction | Destruction commensurate with biofilm deposits | Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies) |
| **Grade modifiers** | Risk factors | Smoking | Non-smoker | Smoker <10 cigarettes/day | Smoker ≥10 cigarettes/day |
| | | Diabetes | Normoglycemic/ no diagnosis of diabetes | HbA1c <7.0% in patients with diabetes | HbA1c ≥7.0% in patients with diabetes |
| **Risk of systemic impact of periodontitis**[a] | Inflammatory burden | High sensitivity CRP (hsCRP) | <1 mg/L | 1 to 3 mg/L | >3 mg/L |
| **Biomarkers** | Indicators of CAL/bone loss | Saliva, gingival crevicular fluid, serum | ? | ? | ? |

**Figure 2.6.** Periodontitis grades (48)

HbA1c; glycated hemoglobin, hsCRP; high sensitivity C-reactive protein, PA; periapical, CAL; clinical attachment loss.

[a] Refers to increased risk that periodontitis may be an inflammatory co-morbidity for the specific patient. Cells in the last two rows shown in gray in the table may be added in the future. These factors need to be substantiated with specific evidence in the future

## 2.4. Oral Health-related Quality of Life (OHRQoL)

Recently, the assessment of the impact of health on QoL has been increasing and is recognized as a crucial component for evaluating public health care outcomes in both medicine and dentistry (58). Measuring how oral diseases affect human life is as important as measuring their incidence and prevalence (59). OHRQoL is the patient's own perception of how their personal oral health affects their well-being (60). Evaluation of OHRQoL is essential in clinical practice to determine treatment needs (61). The growing awareness that QoL is an important outcome of dental care has led to the need for a variety of tools to measure OHRQoL.

The most used approach to measure OHRQOL is multi-item questionnaires. Among these questionnaires, the Oral Health Impact Profile (OHIP) with 49 questions and its short form OHIP-14 with 14 questions or items are widely used (61, 62). OHIP index system was developed by Slade and Spencer in 1994 (63), and its short form was published by Slade in 1997 (60). OHIP-14 evaluates the frequency of oral cavity-related problems on seven domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (60). These domains are derived from the World Health Organization (WHO) International Classification of Impairments, Disabilities and Handicaps (64).

**Table 2.1.** OHIP-14 questionnaire (60)

| **Domains** | **Items** |
|---|---|
| Functional limitation | 1. Have you had trouble pronouncing any words because of problems with your teeth, mouth, or dentures?<br>2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, or dentures? |
| Physical pain | 3. Have you had painful aching in your mouth?<br>4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, or dentures? |
| Psychological discomfort | 5. Have you been self-conscious because of your teeth, mouth, or dentures?<br>6. Have you felt tense because of problems with your teeth, mouth, or dentures? |
| Physical disability | 7. Has your diet been unsatisfactory because of problems with your teeth, mouth, or dentures?<br>8. Have you had to interrupt meals because of problems with your teeth, mouth, or dentures? |
| Psychological disability | 9. Have you found it difficult to relax because of problems with your teeth, mouth, or dentures?<br>10. Have you been a bit embarrassed because of problems with your teeth, mouth, or dentures? |
| Social disability | 11. Have you been a bit irritable with other people because of problems with your teeth, mouth, or dentures?<br>12. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth, or dentures? |
| Handicap | 13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth, or dentures?<br>14. Have you been totally unable to function because of problems with your teeth, mouth, or dentures? |

Adapted from: Slade GD, 1997.

Responses are scored on a Likert-type frequency scale: 0 as “never”, 1 as “hardly ever”, 2 as “occasionally”, 3 as “fairly often” and 4 as “very often”. Separate subscales can be calculated for each domain of the OHIP, while overall levels of impact can be computed by summing the response codes to the 14 items (60). As a result, the total OHIP-14 score ranges from 0 to 56, with higher scores indicating poorer OHRQoL (61).

OHIP-14 questionnaire was validated by performing on Turkish patients (65). In addition, Başol et al. (66) and Balci et al. (67) have reported that Turkish version of OHIP-14 is a valid, reliable, and comprehensible index for measuring OHRQoL in the Turkish population.

There is evidence of a negative association between clinically diagnosed PD and subjectively assessed OHRQoL (5), yet the negative impact of PD may be recovered after periodontal treatment (68). PDs have a greater impact on OHRQoL when the severity or extent of the disease increases (5). Since PD and infertility share common risk factors and both predict health-related psychosocial outcomes (21), their effects may be cumulative. PDs potentially effect QoL in infertile females. Therefore, it is of critical importance to evaluate whether PDs are associated with OHRQoL in infertile females.

### 2.5. Periodontal Medicine

PDs do not only affect periodontium, but also have an impact on the pre-existing systemic conditions and enhance the risk for certain systemic diseases (69-72). The term periodontal medicine, as first suggested by Offenbacher in 1996 (73), is used to describe how PDs may affect systemic health (74).

Periodontitis has been associated with more than fifty systemic conditions and diseases (75). The impact of PD on cardiovascular diseases (76-78), cerebrovascular diseases (79), respiratory diseases (80, 81), diabetes (82-85), and metabolic syndrome (86) are documented. Pre-existing PD can cause adverse pregnancy outcomes such as preterm birth (<37 weeks), low birth weight babies (<2500 grams), gestational diabetes, pre-eclampsia, and fetal loss (87-94). Systemic conditions or diseases such as obesity (95, 96), kidney diseases (97, 98), rheumatoid arthritis (99, 100), inflammatory bowel disease (101), osteoporosis (102, 103), cancer (104, 105), cognitive impairment (106, 107), and Alzheimer's disease (108, 109) are other diseases whose association with PD has been scientifically confirmed with an increasing interest.

Studies on periodontal medicine have led to the revival of the focal infection concept. The idea that there may be a link between oral infection and systemic disease goes back more than a century. In 1891, Miller (110) challenged the assumption that oral infection was limited to the mouth, suggesting that the oral cavity was the focus of infections that could spread to other parts of the body and cause or affect a systemic disease. Thus, the focal infection theory arose (110). In 1900, in addition to caries, periapical abscesses, and pulpal necrosis, Hunter identified PDs as foci of infection and designated it with the term "oral sepsis" (111). By the 1940s, this theory was discarded after it was observed that these observations lacked the rigor of modern scientific studies (112-114). After Miller's historical article on focal infection (110), various studies investigating the possible interactions between oral infections and systemic conditions have been published (79, 83, 113-116).

The ulcerated epithelium lining in the periodontal pocket provides a direct passage of bacteria and their products into the systemic circulation causing bacteremia (117). Bacteremia is common after dental procedures such as subgingival instrumentation, but also arises from normal daily activities such as mastication and oral hygiene measures (117, 118). Periodontal pathogens have been detected in atheromatous plaques (119-121), lungs (19, 122, 123), and placenta (124, 125). In the context of adverse pregnancy outcomes of PDs, invasion of amniotic fluid and fetoplacental unit by periodontal pathogens may cause intrauterine growth restriction or inflammatory acceleration leading to preeclampsia or myometrial contraction, which may result in preterm labor (75, 126).

The role of systemic spread of locally produced inflammatory mediators in periodontal tissues and the systemic effects of the host immune-inflammatory response to periodontal bacteria or their by-products in the systemic circulation have been demonstrated (75, 127-131). Bacteria entering the systemic circulation can react with antibodies and cause various immune inflammatory reactions (132, 133). Periodontal infection-induced proteolytic enzymes and cytokine toxins (e.g., tumor necrosis factor-$\alpha$, interleukin-1$\beta$, prostaglandin) destroy the surrounding periodontal tissue, and cause silent systemic inflammation (73, 82, 134). It has also been proved that CRP levels are increased in periodontitis patients (135, 136). Therefore, as a source of chronic inflammation, PD may affect the pathogenesis of other inflammatory-based diseases such as cardiovascular disease, type 2 diabetes, and endometriosis by increasing CRP levels (75, 135-138).

Besides, PD may affect the pathogenesis of other inflammatory-based diseases by sharing common risk factors such as smoking, stress, diet, aging, race, and gender with other specific systemic diseases (131, 139).

More recently, PD has been associated with erectile dysfunction (140, 141) and male infertility in men (8, 11, 16, 17, 19), while it has been also associated with endometriosis (137, 138), polycystic ovary syndrome (PCOS) (142-144), and female infertility (9, 10, 12-15, 20, 23) in women.

### 2.6. Infertility and In Vitro Fertilization

According to WHO and International Committee for Monitoring Assisted Reproductive Technology, infertility is the inability to achieve a natural pregnancy after 12 months or more of regular unprotected sexual intercourse (24, 145). The infertility rate is increasing, affecting more than 186 million people with different rates according to the developmental level of the country (146). 14.3% of couples are affected from infertility in the western world, while 25% of couples are affected in developing countries (146). Infertility is found 10–15% of women, while in the remaining 80–85%, natural conception occurs in 12 months (147). It is most common in women between the ages of 30-40 (147).

About 1 out of every 8 women between the ages of 15-49 receive infertility treatment (148). IVF is one of the most commonly used treatments to overcome infertility and achieve conception (10). IVF treatment begins with ovarian hyperstimulation through the administration of fertility medications such as gonadotropins. After gonadotropin stimulation, multiple mature ovarian follicles are retrieved from the ovary with an ultrasound-guided needle. The collected oocytes are fertilized with sperm in vitro. Thereafter, the resultant embryo(s) are cultured under optimal conditions, then transferred into the recipient uterus using ultrasound (148).

Infertility can cause various psychological-emotional disorders, such as sadness, anxiety, and stress (149). Infertility is also associated with a high risk of adverse pregnancy outcomes such as preterm labor and pre-eclampsia (150).

Infertility can be classified as primary or secondary infertility. While primary infertility indicates women who have never been pregnant before, secondary infertility is the inability to become pregnant again after giving birth before (151).

Infertility evaluation should be initiated in women younger than 35 years of age who are unable to conceive after 1 year of unprotected intercourse. If the female partner is older than 35 years and has not conceived for 6 months, earlier evaluation should be initiated while more immediate evaluation is necessary for females older than 40 years (152). Diagnostic testing for infertility is also indicated, regardless of age, for women with oligomenorrhea and amenorrhea and in women at high risk for infertility (e.g., previous ovarian surgery, history of chemotherapy or pelvic radiation, family history of early menopause) (148).

Since infertility etiology can be related to abnormalities in the female and/or male reproductive system, both male and female partners should be evaluated when infertility is considered (148). Infertility is caused by abnormalities in physiology or underlying disease in 85% of the infertility cases (153). In 15% of the infertility cases the etiology remains unexplained despite extensive research showing normal ovarian reserve, normal semen parameters, normal ovulation, and a normal endometrial cavity (145).

The most common causes of female infertility are (153-155):

- Dysfunctions of the ovulatory process
- Diminished ovarian reserve
- Anatomical conditions affecting uterus or fallopian tubes
- Endometriosis

Approximately 25% of infertility diagnoses are associated with ovulatory dysfunction. Ovulatory dysfunction may be a manifestation of PCOS, thyroid disorders and hyperprolactinemia. PCOS is associated with ovarian dysfunction with excessive androgen secretion, which is further exacerbated by obesity (156). Anovulation should be suspected if menstrual cycles are irregular and shorter than 21 days or longer than 35 days, or if the patient has abnormal uterine bleeding (152).

Ovarian reserve indicates the reproductive potential of a woman with the total number of oocytes in the ovaries and oocyte quality (148). Diminished ovarian reserve

can cause infertility. Ovarian reserve decreases with history of ovarian surgery, advanced age, chemotherapy, and radiation therapy exposure to the ovaries (148).

Distortion or blockage of the fallopian tubes or failure of the tubes to pick up an oocyte from the ovary due to pelvic inflammatory disease may lead to infertility (157). Endometrial polyps, which are benign overgrowths of the endometrium, can mechanically interfere with sperm transport and embryo implantation, leading to inhibition of conception (158).

Endometriosis, a multifactorial progressive pelvic inflammatory disease, is also a potential cause of infertility and it occurs when endometrial tissue arises outside the uterine cavity (159). Since both endometriosis and PDs are chronic inflammatory diseases, a cause-effect relationship has been proposed, in which an altered inflammatory response to periodontally pathogenic bacteria may lead to the development of endometriosis (137).

Infertility is widely affected by age, though other risk factors including lifestyle and environmental factors are present (146). Young or advanced maternal age (<17 or >34 years), smoking, alcohol and drug abuse, low socioeconomic status, hypertension, diabetes, obesity, sexually transmitted diseases, history of previous preterm birth, chronic inflammation and infections are risk factors for infertility (154). It has been reported that ovarian reserve is diminished in smokers and ovarian response is decreased in smokers undergoing IVF treatment (160). Obesity is a risk factor for infertility associated with anovulation and reduces the chances of spontaneous conception (161). Obese women have lower live birth rates following IVF treatment (162).

Primary indications for IVF include cases of diminished ovarian reserve, ovulatory dysfunction, severe endometriosis, tubal obstruction, severe male factor infertility, and unexplained infertility (163). IVF is the most effective first-line infertility treatment for females older than 35 years with tubal disease, for females older than 38-40 years, for couples with multifactorial infertility and for couples with unexplained infertility (163).

## 2.7. Infertility Parameters

Endocrine events in the menstrual cycle are essential for successful oocyte development, ovulation, fertilization, and implantation (164). Various hormones play a role in regulating the reproductive system and maintaining fertility (165).

Ovarian reserve and anticipated response to IVF treatment can be evaluated with serum endocrine markers such as FSH, E2 and AMH levels (148, 166, 167). In addition, evaluation of AFC by transvaginal ultrasonography is widely used as a potential marker of ovarian reserve and for prediction of ovarian response to treatment (148, 167, 168). Besides, the etiology of infertility can be determined with laboratory testing of these parameters (148, 169).

FSH is secreted by pituitary gland (148). As the size of the follicle pool decreases, the inhibition of FSH secretion by E2 disappears and early follicular phase serum FSH increases. As ovarian reserve decreases further, early follicular phase E2 increases and inhibits FSH elevation (170). FSH values ≥15 mIU/mL indicates diminished ovarian reserve and has been reported be predictive of poor pregnancy outcome (148, 171).

E2 is another steroid hormone secreted by developing ovarian follicles and used for evaluation of ovarian reserve, its levels are usually assessed early in the menstrual cycle, on day 3. E2 levels ≥80 pg/mL on day 3 are associated with poor ovarian response and lower pregnancy rates (148).

AMH, a type of glycoprotein secreted by growing follicles, indicates the ovarian reserve and associates with the number of oocytes retrieved after ovarian stimulation (170, 172). AMH levels may decrease with age and obesity (170, 172) while increasing in adolescents and PCOS cases (173, 174). AMH level can be assessed throughout the menstrual cycle as it is in constant concentration throughout the cycle (148, 175). AMH has been suggested as a better predictor of response to ovarian stimulation than day-3 FSH or E2 levels and its lower levels may indicate low ovarian reserve (176). AMH levels below 1.1 ng/mL can be a marker for a poor ovarian response and lower pregnancy rates (177, 178). Hyper-response is predicted with an increased risk for ovarian hyperstimulation syndrome when the AMH level is higher than 3 ng/mL (177). Ovarian hyperstimulation syndrome, which is characterized by cystic growth of the ovaries, is an iatrogenic complication of ovarian stimulation (179).

AFC is another test that can help predict how many mature oocytes could be retrieved after stimulation, prior to IVF treatment (168, 180). The number of follicles with a diameter of 2-10 mm in the ovaries in the early follicular phase refers to AFC (181). Although some effort has been exerted to standardize the methodology (182) for the AMH levels and the AFC values, its interpretation in literature is still on debate. AFC cut-off value of 3 to 7 demonstrates a significantly diminished ovarian reserve and poor ovarian response to IVF treatment (25, 183-188). AFC value of 14 may be considered above the expected values (177).

It is crucial to evaluate these infertility parameters before the patient enters the IVF program (25).

### 2.8. Association Between Periodontal Diseases and Infertility

In recent years, studies have investigated the relationship between PDs and male (7, 8, 11, 16-19) and female infertility (9, 10, 12, 13, 15, 20, 22, 23, 189).

Periodontitis has been linked with both erectile dysfunction (140, 141, 190) and male infertility (17). The first study examining the relationship between male infertility and PD was performed by Bieniek and Riedel (7). The study suspected a link between bacterial colonies in dental foci and therapy-resistant bacteriospermia. Improvements were observed in semen parameters after periodontal treatment (7). Klinger et al. (8) examined the association between infertility parameters and the periodontal status of males attending IVF clinic and reported that deep periodontal pockets and higher CAL were associated with sperm sub-motility. Nwhator et al. (11) found a relationship between poor oral hygiene and subnormal sperm count. A study by Práger et al. (16) showed that the ratio of calculus and BOP was significantly higher in men with idiopathic infertility. More recently, PD has found to be associated with semen abnormalities (18, 19).

It is crucial to investigate the relationship between PD and female infertility, drawing parallels with male infertility. It has been proven that there is a significant relationship between reproductive failure and a history of vaginal infection (27). Considering that PDs, which are chronic infections, cause adverse pregnancy outcomes, it can be suggested that they may affect fertility, pregnancy, and the outcome of infertility treatment due to bacteremia, endotoxemia and increased plasma inflammatory cytokine levels (31).

Although the relationship between infertility and periodontal status in infertile women has a new field of research, the effect of IVF treatment on periodontal status has been investigated by various researchers (10, 13, 31, 191, 192). Studies reported that infertility treatment exacerbates gingival inflammation and PD process. According to Haytac et al. (31), ovulation induction exacerbates gingival bleeding and gingival crevicular fluid volume in direct proportion to the duration of use. Ovulation induction increases serum sex hormones and since there are progesterone and estrogen receptors in the gingiva, infertility treatment causes a change in the gingival vasculature and worsens the gingival inflammation (13, 31).

As the first study to investigate the link between conception and PDs, Hart et al. (9) found a relationship between PD and increased time to conception in non-Caucasion women. This observational study suggested that females with PD takes an extra 2 months to conceive showing that PD as modifiable risk factor for conception. Building on this study, Nwhator et al. (12) similarly found that poor oral hygiene and periodontitis were associated with an increased time to conception in Nigerian pregnant women. In another observational study, Paju et al. (15) reported that increased level of Porphyromonas gingivalis, a periodontally pathogenic gram negative bacteria, and high concentrations of salivary antibodies may play a role in delayed conception.

There are cross-sectional case-control studies comparing the periodontal status of fertile and infertile women in the literature (13, 20, 23) Lalasa et al. (13) reported that CAL in infertile women was found statistically significantly higher compared to fertile women. Telatar et al. (23) stated that infertile female group showed higher mean values of probing pocket depth (PPD), CAL, gingival index (GI), BOP and higher periodontitis prevalence compared to fertile female group, while mean plaque index (PI) was not statistically different between groups. In another study, Machado et al. (20) investigated the periodontal status and OHRQoL in both infertile females who were seeking infertility treatment and in matched fertile females. Infertile females showed higher prevalence and severity of PD compared to fertile counterparts. However, PD did not affect OHRQoL in infertile group, suggesting ignorance and unawareness about PDs in women seeking infertility treatment.

Drawing parallels with the impact on infertility and duration of conception, the effect of PD on the outcome of IVF treatment was also studied (10, 22, 189). These studies

investigated the relationship between pre-existing periodontal status and IVF outcome parameters.

Pavlatou et al. (10) conducted the first study examining the relationship between periodontal status and IVF outcome parameters in infertile women. Clinical periodontal examination and blood tests were performed on 60 infertile women and repeated after IVF treatment and on the day of pregnancy test. Simplified GI, plaque control recording index, PPD and BOP measurements only for periodontitis were performed as clinical periodontal parameters and periodontal status of the patients was diagnosed. IVF outcome parameters (E2 levels, follicle numbers, numbers of transferred embryos) were also examined. In addition, the success of the IVF treatment as achievement of pregnancy, was also examined in all periodontal groups. It was concluded that periodontal status had no effect on IVF success. However, negative correlations between the number of follicles and GI before IVF, and the number of transferred embryos and GI after IVF were found in all women. After IVF treatment, a negative correlation was recorded between BOP and both the follicle and transferred embryo numbers in periodontitis patients. Therefore, according to Pavlatou et al., women with pre-existing periodontal inflammation seem to have worse IVF outcome parameters, although not reflected on the achievement of pregnancy. In the light of the study by Pavlatou et al. (10), Khalife et al. (182) (2019) and Altaş et al. (22) (2020) performed similar studies.

A pilot study conducted by Khalife et al. (182) examined 34 infertile women before and after their IVF treatments to evaluate whether PD has any effect on the parameters of IVF outcome. As clinical periodontal measurements, plaque and bleeding indices were recorded. PD was classified according to the AAP classification (193). The number of retrieved, mature, and fertilized oocytes, as well as transferred embryos, were recorded as IVF outcome parameters. Besides, CRP levels of the patients were determined before entering IVF program. None of the women included in this study were diagnosed with periodontitis. All patients had varying degrees of gingivitis. Periodontal parameters and gingivitis status did not significantly affect any IVF outcome parameters and live birth rates. Plaque and bleeding indices were not statistically significantly lower in patients who achieved pregnancy after IVF treatment. Although not reaching statistical significance, CRP levels were higher in patients with positive IVF outcomes. The evidence presented by this study could not support the hypothesis that PD is correlated with poor IVF outcome parameters.

The study of Altaş et al. (22) examined 103 infertile women undergoing IVF treatment to evaluate the effect of periodontal status on IVF outcome parameters by considering the serum E2 and progesterone levels, the number of oocyte and transferred embryos and the achievement of pregnancy. After sociodemographic data collection, PI, GI, PPD and BOP were measured and the subjects were classified into periodontally healthy, gingivitis, and periodontitis groups. These groups were compared with respect to E2 and progesterone levels, the number of oocyte and transferred embryos, and pregnancy rates. PD status groups were statistically similar in terms of retrieved oocytes, transferred embryos and pregnancy rates. Although the three groups were statistically similar regarding E2 levels on the day of pregnancy testing, progesterone levels were significantly higher in the periodontitis group compared to the periodontally healthy and gingivitis groups.

Similar to PD prevalence in the world (51), infertility is increasing recently (146). Even with significant advancements in the treatment of infertility, implantation failure remains frequent. This fact demonstrates that new parameters need to be explored for IVF treatments such as periodontal health and disease (14).

# 3. MATERIAL AND METHODS

The study was approved by the scientific committee of Yeditepe University Faculty of Dentistry (397/01/2021) and the ethical board of Yeditepe University (1422/04/2021) with compliance with the Declaration of Helsinki (Appendix 1).

## 3.1. Patient Selection

The individuals involved in this study were selected among the patients who applied Yeditepe University, Faculty of Medicine, Department of Obstetrics and Gynecology, IVF Clinic between May 2021, and July 2022. Infertile female patients who attended to IVF Clinic were referred to the Yeditepe University, Faculty of Dentistry, Department of Periodontology. Patient inclusion and exclusion criteria for the study is shown in Table 3.1.

**Table 3.1**. Inclusion and exclusion criteria for the study

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Presence of at least 20 teeth<br>• No systemic disease<br>• No periodontal treatment within 12 months<br>• No use of systemic antibiotic, immunosuppressive and/or corticosteroids in the last 6 months<br>• Not receiving any infertility treatment in the past 6 months<br>• Having an ovulatory cycle | • Lack of consent by patient<br>• Systemic diseases<br>• History of periodontal treatment in the last 12 months<br>• Systemic antibiotic, immunosuppressive and/or corticosteroids use within the last 6 months<br>• Non-Turkish<br>• Male factor responsible for infertility<br>• Women with endometriosis<br>• Women with PCOS |

Patients who met the inclusion criteria were invited to participate in the study. Written informed consent was obtained from all participants after the objectives of this study were explained in a comprehensive manner (Appendix 2).

### 3.2. Study Design

This research is designed as cross-sectional descriptive study. The flow of the study is shown in Figure 3.1. All participants underwent a gynecological examination at Yeditepe University, Faculty of Medicine, Department of Obstetrics and Gynecology, IVF Clinic. Blood tests were performed before the periodontal examination. Thereafter IVF Clinic referred the infertile female patients to the Yeditepe University, Faculty of Dentistry, Department of Periodontology prior to their IVF treatments. After completing two different questionnaires, a comprehensive periodontal examination was performed.

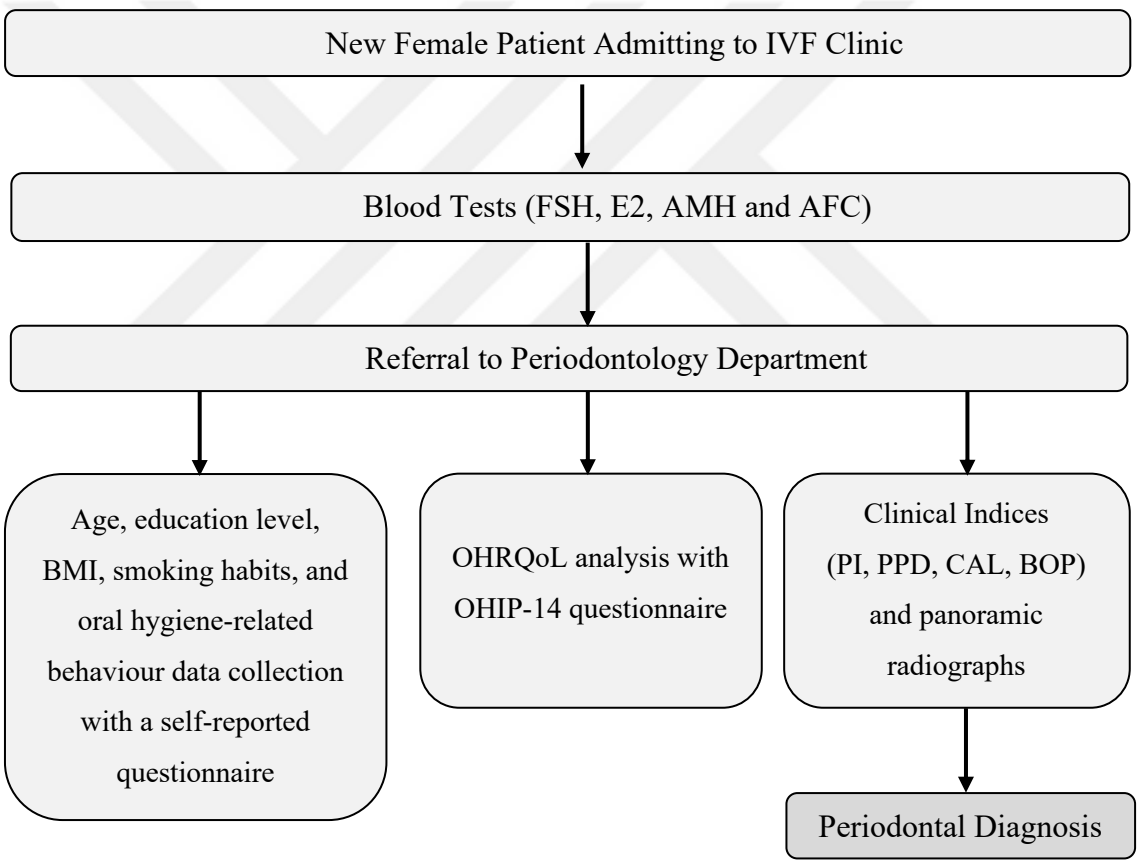


**Figure 3.1.** The flow chart of the study

AFC; Antral Follicle Count, AMH; Anti-Müllerian Hormone, BMI; Body Mass Index, BOP; Bleeding on Probing, CAL; Clinical Attachment Level, E2; Estradiol, FSH; Follicle-Stimulating Hormone, OHIP; Oral Health Impact Profile, OHRQoL; Oral Health-related Quality of Life, PI; Plaque Index, PPD; Probing Pocket Depth

### 3.3. Assessment of Infertility Parameters

Prior to IVF treatment, patients underwent gynecologic examinations and blood tests. Serum FSH, E2 and AMH levels were evaluated. AFCs were evaluated by using ultrasound. All gynecological examinations and evaluation of blood tests were performed by the same examiner (NEA) in the IVF clinic.

- The FSH levels were grouped as <15 mIU/L (expected normal values), and ≥15 mIU/L (poor ovarian response and pregnancy outcomes) (148, 171).
- The E2 levels were grouped as E2 <80 pg/mL (expected normal values), and ≥80 pg/mL (poor ovarian response and pregnancy outcomes) (148).
- The AMH levels were grouped as <1.1 ng/mL (poor ovarian response and pregnancy outcomes), 1.11-3 ng/mL (expected normal values), and >3 ng/mL (hyper-response potential) (177, 178).
- The AFC values were grouped as <7 (poor ovarian response and pregnancy outcomes), 7-14 (expected normal values) and >14 (above the expected normal values) (148, 177, 183-188).

### 3.4. Data Collection of Age, Education Level, Body Mass Index, Smoking Habits, and Oral Hygiene-related Behaviors

Age, level of education, weight, and height to calculate BMI, information on smoking habits, and oral hygiene-related behaviors of the patients were collected through a standardized self-reported questionnaire (Appendix 3). In the questionnaire:

- The level of education was categorized into five levels:
    - Uneducated
    - Primary school
    - High school
    - University
    - Postgraduate
- BMI was calculated as weight in kilograms divided by the square of height in meters and patients was divided into four groups (194):
    - Underweight was defined as having a BMI below 18.5 kg/$m^2$
    - Normal weight as a BMI of 18.5- 24.9 kg/$m^2$
    - Overweight as a BMI of 25 to 29.9 kg/$m^2$

    - Obese as a BMI over 30 kg/$m^2$

- Smoking consumption was categorized into four groups (20, 48):
    - Non-smoker
    - Former smoker
    - Smoker <10 cigarettes per day
    - Smoker ≥10 cigarettes per day

- Behaviors related to oral hygiene was assessed under three categories as (22):
    - Tooth brushing frequency (never/ once a day/ twice a day/ irregular)
    - Interproximal cleaning (never/ once a day/ twice a day/ irregular)
    - Mouth rinse consumption (yes/ no)

### 3.5. Oral Health-related Quality of Life (OHRQoL) Assessment

Before the clinical periodontal examination, self-perceived OHRQoL was assessed using OHIP-14 questionnaire (60). The validated Turkish version of the OHIP-14 questionnaires (66) were completed by each patient (Appendix 4).OHRQoL was evaluated in seven domains as described below:

- Functional Limitation (items 1 and 2)
- Physical Pain (items 3 and 4)
- Psychological Discomfort (items 5 and 6)
- Physical Disability (items 7 and 8)
- Psychological Disability (items 9 and 10)
- Social Disability (items 11 and 12)
- Handicap (items 13 and 14)

Responses were made on a 5-point Likert-type scale and coded as described by Slade (60):

- 0: never
- 1: hardly ever
- 2: occasionally
- 3: fairly often
- 4: very often

The OHIP-14 total scores were calculated by summing the coded responses of 14 items within each domain. The higher scores indicate worse OHRQoL.

### 3.6. Periodontal Assessment

#### 3.6.1. Clinical Measurements

Clinical indices and measurements were performed including PI, PPD, CAL, and BOP by the same calibrated examiner (NK), using a 0.4 mm diameter 15 mm calibrated manual periodontal probe[#] (Figure 3.2). The measurements were performed at six sites on each tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, and disto-lingual) except third molars, implants and retained roots if any. Prior to the study, the intra-examiner agreement was tested by repeated measurements of periodontal clinical parameters on 10 patients at one-hour intervals (ICC:0.99) (95% CI; 0.99-1.00).

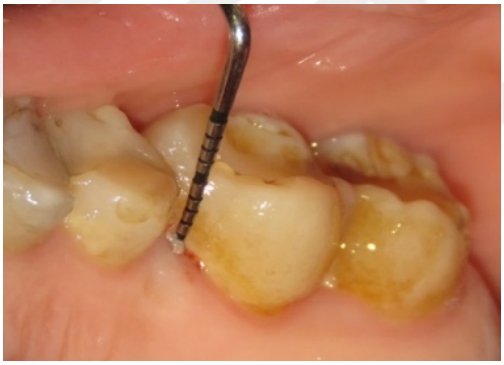

**Figure 3.2:** A photograph representing clinical measurements with University of North Carolina PCPUNC15 probe

Measurements were recorded to the Yeditepe University Department of Periodontology measurement chart (Figure 3.3).

[#] University of North Carolina PCPUNC15, Hu Friedy Ins Co., USA

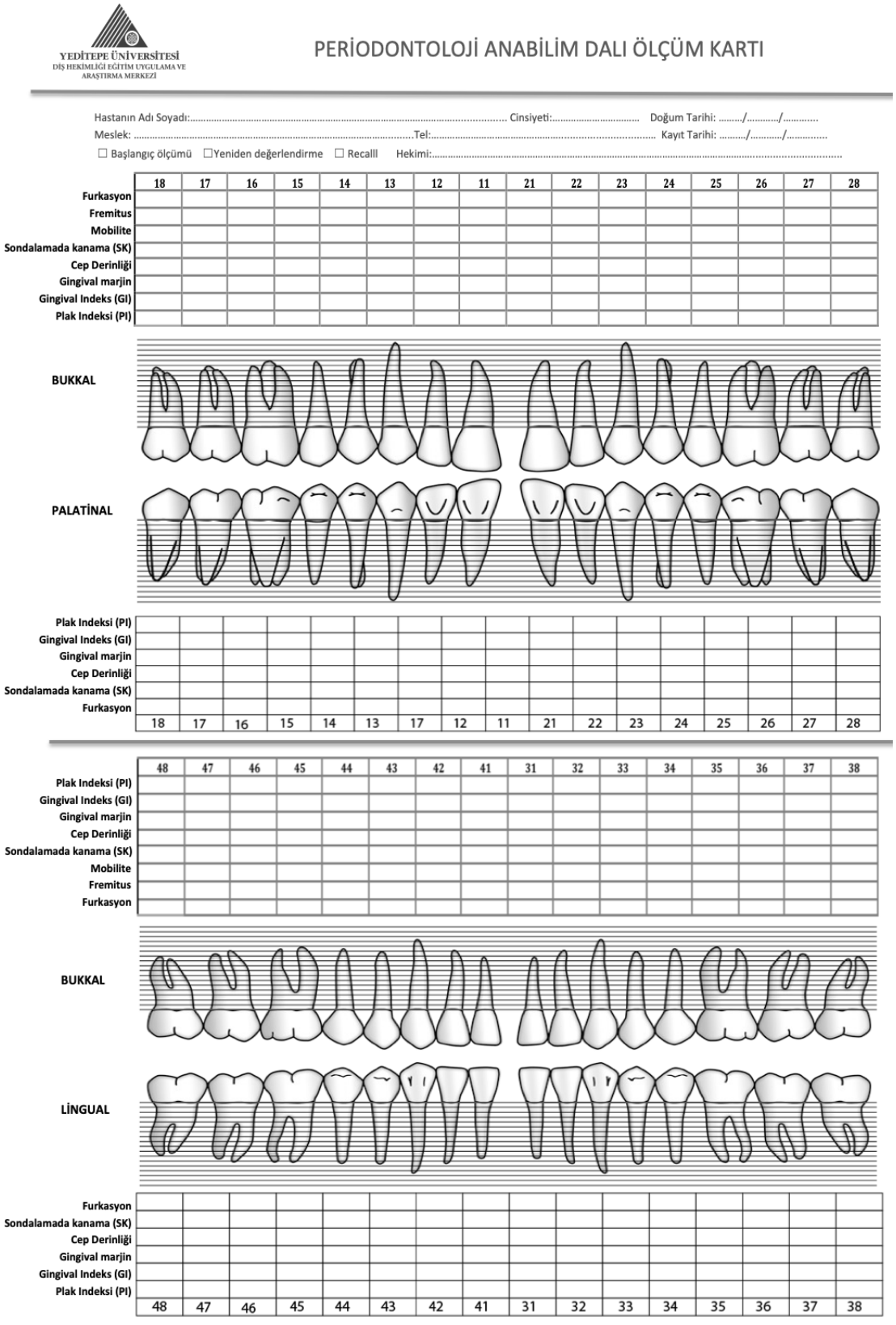


**Figure 3.3.** Yeditepe University Department of Periodontology measurement chart

#### 3.6.1.1. Plaque Index (PI)

After the teeth were dried by air syringe, microbial dental plaque biofilm was evaluated with the probe from six tooth surfaces and full mouth PI was recorded on a 0–3 scale (195). Scoring criteria of PI is shown in Table 3.2.

**Table 3.2.** Plaque Index scores (195)

| | |
|---|---|
| **0** | No microbial dental plaque in the gingival area |
| **1** | A film of microbial dental plaque adhering to the free gingival margin and adjacent area of the tooth, recognized only by running a probe across the tooth surfaces |
| **2** | Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and/or adjacent tooth surfaces that can be seen by naked eye |
| **3** | Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface |

#### 3.6.1.2. Probing Pocket Depth (PPD)

Full mouth PPD was measured by the periodontal probe from six tooth surfaces as the distance between the gingival margin and the bottom of the gingival sulcus.

#### 3.6.1.3. Clinical Attachment Level (CAL)

Full mouth CAL was measured by the periodontal probe from six tooth surfaces as the distance between the CEJ and the bottom of the gingival sulcus.

#### 3.6.1.4. Bleeding on Probing (BOP)

BOP was assessed simultaneously to the probing measurements, and absence or presence of bleeding up to 30 seconds after probing was recorded from six tooth surfaces and scored as positive (+) or negative (-) bleeding for each point (196). The percentage of BOP was calculated by dividing the number of bleeding sites by the total number of sites measured.

### 3.6.2. Periodontal Diagnosis

After clinical indices and measurements were performed, panoramic radiographs were taken from each patient for periodontal diagnosis. PD classification was based on the EFP/AAP 2018 classification of Periodontal Diseases and Conditions (3, 4, 40, 48, 57).

Recruited patients were classified into the periodontally healthy, gingivitis, and periodontitis groups (PD status groups). Periodontitis cases were further classified using staging and grading system.

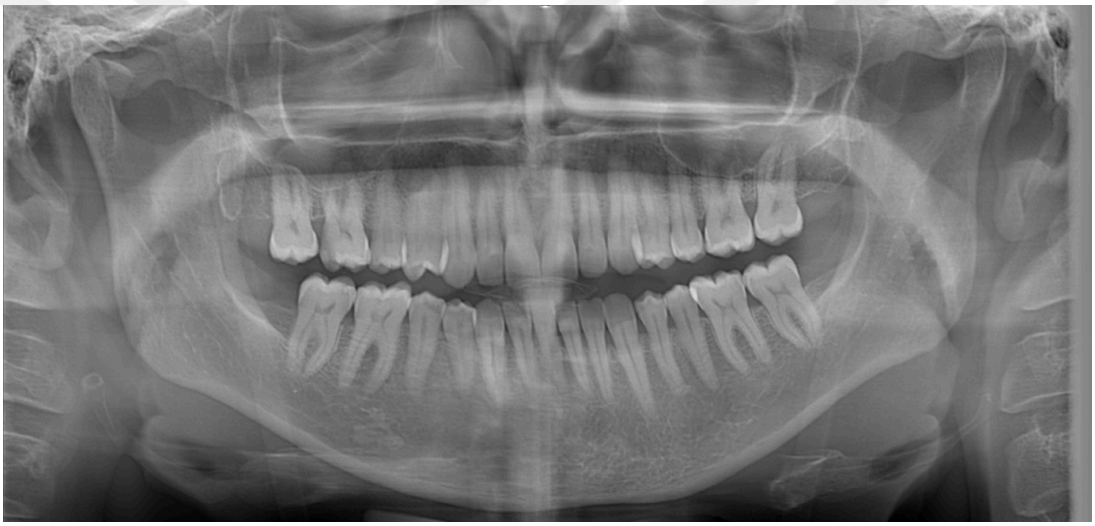

**Figure 3.4.** A representative panoramic radiograph of a localized Stage I Grade B periodontitis patient

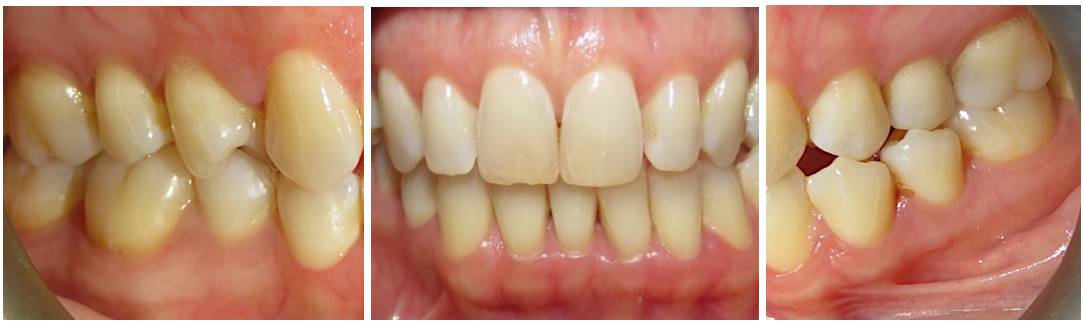

**Figure 3.5.** Representative intra-oral photographs of a localized Stage I Grade B periodontitis patient

### 3.7. Statistical Analysis

Statistical analysis was performed using the SPSS (Statistical Packages of Social Sciences) version 25 software package (IBM, Armonk, NY, USA) and a value of $p<0.05$ was considered to be statistically significant. Age, education level, BMI, smoking habits, and oral hygiene-related behaviors were evaluated in all patients. PD status groups were compared with respect to both clinical periodontal parameters (PI, PPD, CAL, BOP) and infertility parameters (FSH, E2, AMH levels, and AFC values) in each patient. For OHRQoL assessments, the OHIP-14 scores were evaluated in all patients and compared with PD status.

Continuous variables were recorded as the mean value ± standard deviation (SD) for all investigated parameters. Categorical variables were expressed as numbers (n) and percentage (%). The compliance of parameters to the normal distribution was evaluated using Levene test.

In order to determine whether the equal number of patients would have been necessary to analyze distribution of the periodontal classification (PD status), Chi-Square test was applied to compare current and equally distributed number of patients.

In the comparisons of the patient characteristics (age, education level, BMI, smoking habits, and oral hygiene-related behaviors) and PD status, chi-square ($\chi 2$) test was used. Kruskal Wallis test was performed for the comparison of OHIP-14 scores between the PD groups and post-hoc Mann-Whitney U test was performed to test the significance of pairwise differences. The comparison of infertility parameters and PD status was analyzed by one-way ANOVA test. Post hoc Bonferroni test was performed to test the significance of pairwise differences. Correlations between infertility and periodontal parameters were analyzed by Pearson's correlation test.

# 4. RESULTS

The patient population involved in this study was consisted of 65 infertile female patients who were seeking IVF treatment and who met the inclusion criteria of the study.

## 4.1. Patient Characteristics Involved in the Study

### 4.1.1. Age Profile of the Patients

The age ranges of the patients were organized as <36, and ≥36. The patients were between 24-46 years old (mean age=35.68). Age distribution of the patients is shown in Figure 4.1.

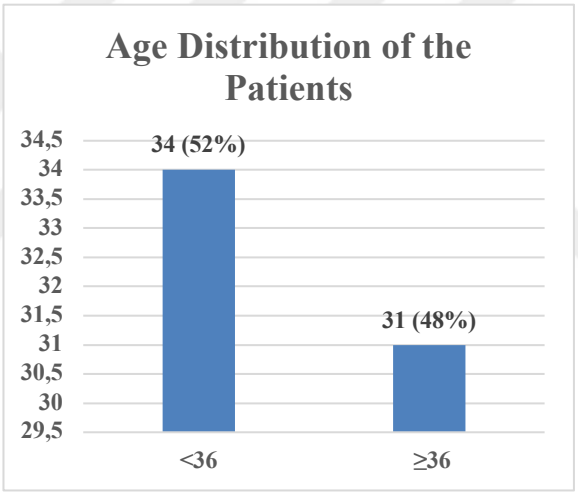


**Figure 4.1.** Age distribution of the patients (data represent number and percentage of the patients)

### 4.1.2. Education Level of the Patients

The level of education of the patients is shown in Figure 4.2. Most of the patients graduated from university (n=39, 60%) followed by high school graduates (n=12, 18%), primary school graduates (n=7, 11%) and postgraduates (n=7, 11%).

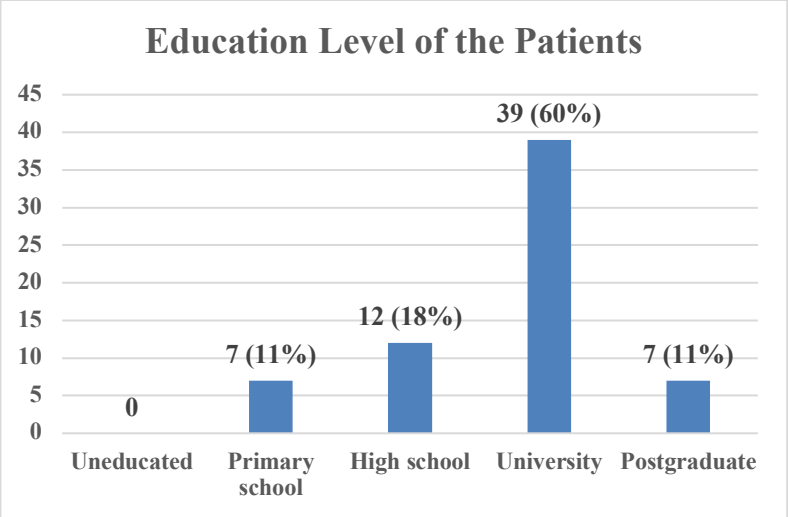


**Figure 4.2.** Education level of the patients (data represent number and percentage of the patients)

### 4.1.3. Body Mass Index of the Patients

In terms of the BMI distribution of the patients, majority of the patients (n=42, 65%) have a normal weight followed by overweight (n=18, 27%), and obese (n=5, 8%). None of the patients in the study group was found underweight. The BMI distribution of the patients is shown in Figure 4.3.

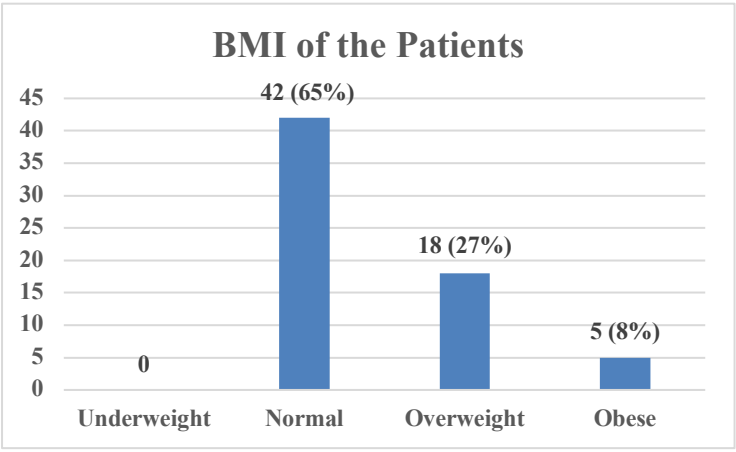


**Figure 4.3.** Body Mass Indices of the patients (data represent number and percentage of the patients)

### 4.1.4. Smoking Habits of the Patients

The number of non-smoker patients was 42 (65%) whereas the number of smokers was 23 (35%) (Figure 4.4). All the smoker patients used less than 10 cigarettes per day.

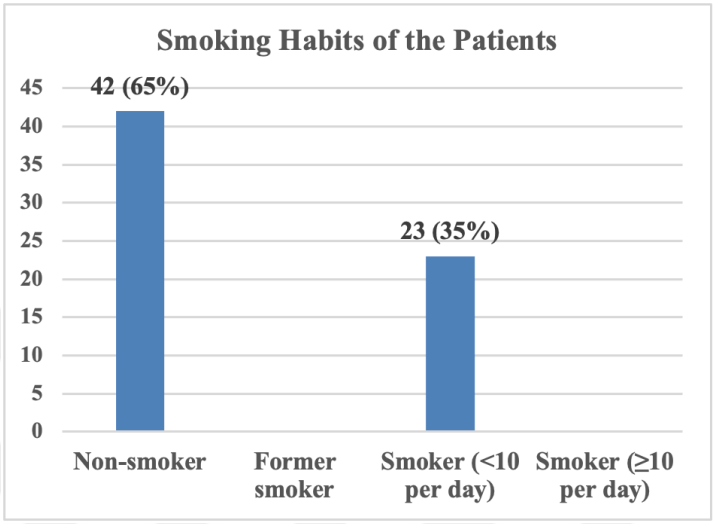


**Figure 4.4.** Smoking habits of the patients (data represent number and percentage of the patients)

### 4.1.5. Oral Hygiene-Related Behavior of the Patients

Considering the oral hygiene-related behaviors of the patients, it has been observed that although most of the patients (n=52, 80%) were brushing their teeth twice a day, interproximal cleaning and mouth rinse consumption were rather infrequent in the study group. Oral hygiene-related behaviors of the patients are presented in Figure 4.5.

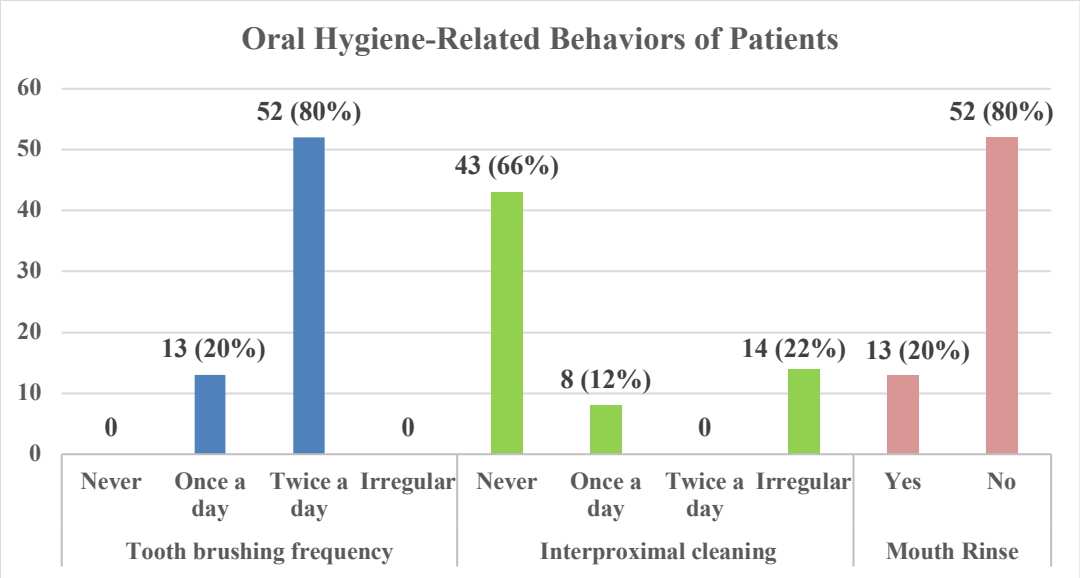


**Figure 4.5.** Oral hygiene-related behaviors of the patients (data represent number and percentage of the patients)

### 4.2. Infertility Parameters

FSH, E2, AMH levels and AFC values as infertility parameters varied between the patients.

FSH values ≥15 mIU/mL indicates diminished ovarian reserve and poor ovarian response to IVF treatment. In line with the level suggested in the literature, 2 periodontitis patients revealed FSH values above 15 (Figure 4.6A) (Table 4.1).

E2 is another hormone used for evaluation of ovarian reserve. E2 levels ≥80 pg/mL are associated with lower pregnancy rates. Eight patients, 1 of which is gingivitis and 7 of which are periodontitis patients, had E2 levels indicating poor ovarian response and pregnancy outcome (Figure 4.6B) (Table 4.1).

AMH, a type of glycoprotein secreted by growing follicles, indicates the ovarian reserve and is related to the number of oocytes retrieved after ovarian stimulation. The AMH levels of patients involved in the study was grouped as <1.1 ng/mL (poor ovarian response and pregnancy outcomes), 1.11-3 ng/mL (expected normal values), and >3 ng/mL (undesirable hyper-response potential). The highest number of the patients (n=44) revealed an undesirable AMH value at <1.11 ng/mL and > 3 ng/mL levels (Figure 4.6C)

(Table 4.1). Five out of 44 patients appeared in gingivitis group whereas the rest was diagnosed as periodontitis.

AFC is another test that can used to predict how many mature eggs could be retrieved after stimulation. The AFC numbers of patients involved in the study was grouped as <7 (n=38) (poor ovarian response and pregnancy outcomes), 7-14 (n=21) (expected normal values), and >14 (above the expected normal values) (n=6) (Figure 4.6D) (Table 4.1).

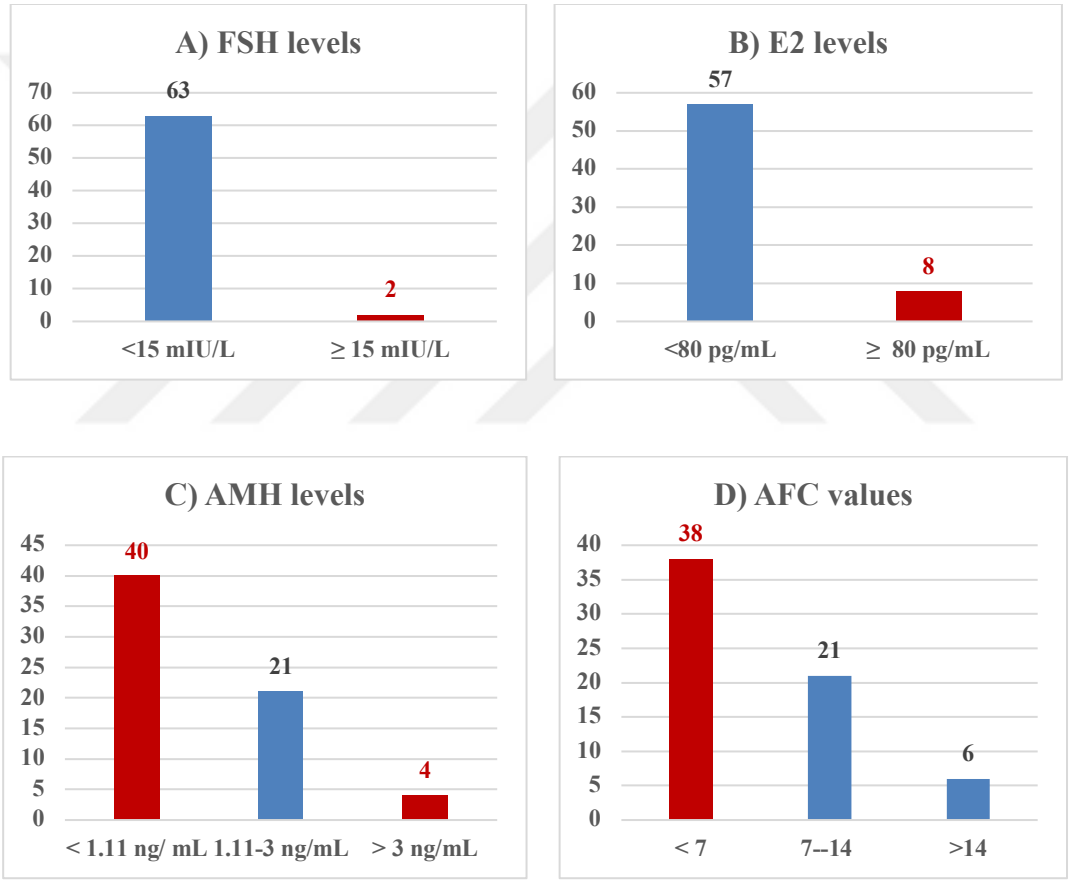


**Figure 4.6.** Infertility parameters of patients involved in the study (data represent number of the patients)

**Table 4.1.** Number of patients presenting undesirable values of infertility parameters according to PD status

| Undesirable infertility parameter values | Gingivitis | LStIGrB Periodontitis | GStIGrB Periodontitis | GStIIGrB Periodontitis |
|---|---|---|---|---|
| **FSH ≥ 15 mIU/mL** | - | - | 1 | 1 |
| **E2 ≥ 80 pg/mL** | 1 | 2 | 1 | 4 |
| **AMH < 1.1 ng/mL and >3 ng/mL** | 5 | 14 | 9 | 16 |
| **AFC < 7** | 4 | 13 | 7 | 14 |

LStIGrB; localized Stage I Grade B, GStIGrB; generalized Stage I Grade B, GStIIGrB; generalized Stage II Grade B

### 4.3. Periodontal Disease Status of the Patients

Periodontal diagnosis distribution of the study population revealed 13 generalized gingivitis, 22 localized Stage I Grade B (LStIGrB) periodontitis, 13 generalized Stage I Grade B (GStIGrB) periodontitis, and 17 generalized Stage II Grade B (GStIIGrB) periodontitis (Figure 4.7). No periodontally healthy patients were detected.

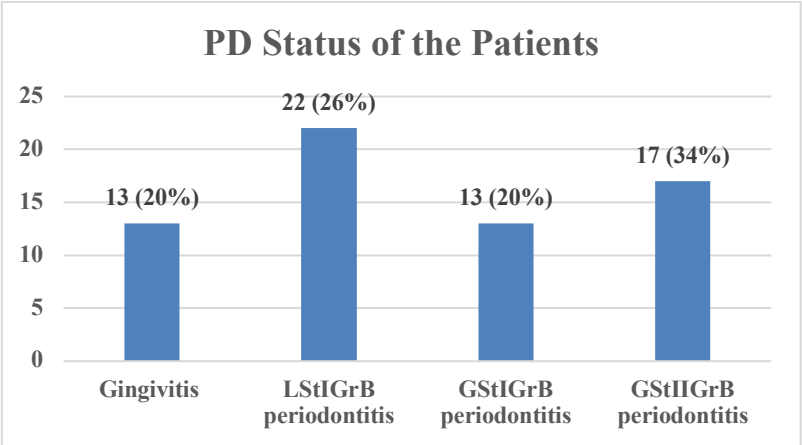


**Figure 4.7.** PD status of the patients (data represent number and percentage of the patients)

In order to determine whether the equal number of patients would have been necessary to analyze distribution of the periodontal classification, Chi-Square test is applied to compare current and equally distributed number of patients and no significant difference was found in between the unequal and equal distribution of patient numbers within the groups (chi-square test statistics= 3.369, p=0.338) (Table 4.2).

**Table 4.2.** Comparison of unequal and equal number of patients in groups

| PD Status | Observed Number | Expected Number | Residual | Test Statistics | |
|---|---|---|---|---|---|
| Generalized Gingivitis | 13 | 16.3 | -3.3 | chi-square | 3.369 |
| LStIGrB Periodontitis | 22 | 16.3 | 5.7 | **p value** | **0.338** |
| GStIGrB Periodontitis | 13 | 16.3 | -3.2 | | |
| GStIIGrB Periodontitis | 17 | 16.3 | 0.8 | | |

## 4.4. Periodontal Parameters and Periodontal Disease Status

The mean values and standard deviations of periodontal parameters as PPD, CAL, BOP and PI according to PD status are shown in Table 4.3.

**Table 4.3.** The mean and standard deviations of periodontal clinical parameter values according to PD status

| Clinical Parameters | Gingivitis | LStIGrB Periodontitis | GStIGrB Periodontitis | GStIIGrB Periodontitis |
|---|---|---|---|---|
| **PPD (mm)** | 2.17 ± 0.41 | 2.55 ± 0.34 | 2.77 ± 0.54 | 3.18 ± 0.51 |
| **CAL (mm)** | 1.94 ± 0.30 | 2.60 ± 0.34 | 3.06 ± 0.70 | 3.39 ± 0.55 |
| **BOP (%)** | 41.52 ± 20.52 | 59 ± 19.60 | 62.07 ± 17.37 | 78.64 ± 13.48 |
| **PI (score)** | 1.26 ± 0.37 | 1.63 ± 0.31 | 1.39 ± 0.38 | 1.76 ± 0.35 |

### 4.5. Association Between Patient Characteristics and Periodontal Disease Status

The association between patient characteristics (age, education level, BMI, smoking habits, and oral hygiene-related behaviors) and PD status was evaluated and presented in Table 4.4.

The number ≥ 36 years old patients (n=16) in the GStIIGrB periodontitis group was statistically significant (p=0.000).

Regarding educational level according to PD status, university graduates constituted most of the patients in the whole study group, followed by high school graduates. However, no statistically significant associations were found between educational levels and the PD status groups.

In all PD status groups, patients with normal BMI were the majority, followed by the overweight patients who are considered as tolerable. There were no underweight patients in all PD status groups, whereas there were 5 obese participants. No statistically significant differences were found between BMI and PD status groups.

Number of non-smokers were higher in all PD status groups and all smoker patients were smoking less than 10 cigarettes per day. None of the patients declared the use of e-cigarettes or water pipes. Number of smokers was highest in periodontitis groups. No statistically significant difference was found between smoking habits and PD status groups.

In all PD status groups, tooth brushing frequency of “twice per day” was found to be the most common brushing habit. None of the patients in these four PD status groups gave the answer of “never” or “irregular” for tooth brushing frequency. Interproximal cleaning and mouth rinse consumption is rather infrequent in all groups. No statistically significant differences were found between the PD status groups in terms of tooth brushing frequency, interproximal cleaning, and mouth rinse consumption.

**Table 4.4.** Comparisons of the patient characteristics (age, education level, BMI, smoking habits, and oral hygiene-related behaviors) according to PD status

| Patient Characteristics | | | Gingivitis | LStIGrB Periodontitis | GStIGrB Periodontitis | GStIIGrB Periodontitis |
|---|---|---|---|---|---|---|
| **Age** | | *<36* | 10 | 15 | 8 | 1 |
| | | *≥36* | 3 | 7 | 5 | 16* |
| **Education Level** | | *Uneducated* | - | - | - | - |
| | | *Primary School* | - | 2 | 2 | 3 |
| | | *High School* | 4 | 3 | - | 5 |
| | | *University* | 8 | 14 | 9 | 8 |
| | | *Postgraduate* | 1 | 3 | 2 | 1 |
| **BMI** | | *Underweight* | - | - | - | - |
| | | *Normal* | 9 | 14 | 8 | 11 |
| | | *Overweight* | 4 | 6 | 3 | 5 |
| | | *Obese* | - | 2 | 2 | 1 |
| **Smoking Habits** | | *Non-Smokers* | 9 | 13 | 9 | 11 |
| | | *Smokers* | 4 | 9 | 4 | 6 |
| **Oral Hygiene Related Behaviors** | *Tooth brushing frequency* | *Never* | - | - | - | - |
| | | *Once a day* | 1 | 4 | 4 | 4 |
| | | *Twice a day* | 12 | 18 | 9 | 13 |
| | | *Irregular* | - | - | - | - |
| | *Inter-proximal cleaning* | *Never* | 7 | 16 | 11 | 9 |
| | | *Once a day* | 4 | 1 | 1 | 2 |
| | | *Twice a day* | - | - | - | - |
| | | *Irregular* | 2 | 5 | 1 | 6 |
| | *Mouth rinse* | *Yes* | 3 | 7 | 3 | 0 |
| | | *No* | 10 | 15 | 10 | 17 |

Chi-square test, *p<0.05

### 4.6. OHRQoL and Periodontal Disease Status

The results of self-perceived OHRQoL, assessed using OHIP-14 questionnaire, are shown in Table 4.5. For the multiple comparison of OHIP-14 scores with PD status, Kruskal Wallis test revealed a significant difference for "functional limitation" domain (p=0.006). Pairwise comparisons revealed that, there were significant differences between GStIIGrB Periodontitis - Gingivitis (p=0.004), GStIIGrB - LStIGrB Periodontitis (p=0.03) and GStIIGrB - GStIGrB Periodontitis (p=0.013), GStIIGrB periodontitis presenting the highest score. There were no significant differences between the PD status groups neither in other individual OHIP-14 domains nor in total OHIP-14 scores.

**Table 4.5.** Comparison of the mean and standard deviations of OHIP-14 scores according to PD status

| OHIP-14 Domains | Gingivitis | LStIGrB Periodontitis | GStIGrB Periodontitis | GStIIGrB Periodontitis |
|---|---|---|---|---|
| **Functional Limitation** | 0.08 ± 0.27 | 0.36 ± 0.79 | 0.15 ± 0.37 | **0.88 ± 0.92**[a*, b*, c*] |
| **Physical Pain** | 2.38 ± 1.38 | 2.41 ± 1.33 | 2.69 ± 0.94 | 2.53 ± 1.54 |
| **Psychological Discomfort** | 3.23 ± 1.30 | 3.23 ± 1.23 | 3.23 ± 1.42 | 2.94 ± 1.43 |
| **Physical Disability** | 0.54 ± 1.39 | 0.68 ± 1.35 | 0.69 ± 0.85 | 0.88 ± 1.05 |
| **Psychological Disability** | 0.92 ± 1.03 | 1.59 ± 1.40 | 1.15 ± 1.40 | 1.35 ± 1.45 |
| **Social Disability** | 0.46 ± 0.77 | 0.59 ± 1 | 0.38 ± 0.90 | 0.77 ± 0.92 |
| **Handicap** | 1.15 ± 1.06 | 1.55 ± 1.73 | 0.92 ± 0.95 | 1.94 ± 1.24 |
| **Total OHIP-14 Score** | 8.77 ± 4.81 | 10.36 ± 6.36 | 9.23 ± 3.91 | 11.12 ± 5.85 |

Kruskal Wallis test, Post hoc by Mann-Whitney U test, *p< 0.05

[a]comparison with gingivitis, [b]comparison with localized Stage I Grade B periodontitis, [c]comparison with generalized Stage I Grade B periodontitis

### 4.7. Infertility Parameters and Periodontal Disease Status

The mean values and standard deviations of four infertility parameters; FSH, E2, AMH and AFC in patients diagnosed with four different PD status are given in Table 4.6.

Although an increase was seen in the mean values of FSH and E2 starting from gingivitis up to GStIIGrB periodontitis, no significant differences were detected in multiple comparisons (p=0.078 and p=0.357, respectively). However, for AMH and AFC parameters significant differences were found between the PD status groups (p=0.027 and p=0.005, respectively).

Pairwise comparisons revealed that, both AMH levels and AFC values were significantly lower in GStIIGrB periodontitis group compared to gingivitis group (p=0.029 and p=0.003, respectively).

**Table 4.6.** Comparison of the mean and standard deviations of the infertility parameters according to the PD status

| Infertility Parameters | Gingivitis | LStIGrB Periodontitis | GStIGrB Periodontitis | GStIIGrB Periodontitis |
|---|---|---|---|---|
| **FSH** | 6.67 ± 2.20 | 8.03 ± 3.34 | 10.22 ± 3.60 | 10.74 ± 7.62 |
| **E2** | 39.16 ± 20.01 | 53.91 ± 49.15 | 46.35 ± 15.78 | 70.32 ± 66.01 |
| **AMH** | 1.80 ± 2.04 | 1.42 ± 1.32 | 1.09 ± 0.83 | **0.44 ± 0.30**[a*] |
| **AFC** | 10.46 ± 6.09 | 7.32 ± 5.60 | 8.08 ± 4.85 | **3.53 ± 2.15**[a*] |

One-way ANOVA test, Post hoc by Bonferroni test, *p<0.05

[a*]significance between generalized Stage II Grade B periodontitis and gingivitis

### 4.8. Correlation of Periodontal and Infertility Parameters

Correlations between periodontal and infertility parameters according to PD status are represented in Table 4.7. For correlation analysis, patients were considered in 3 new PD status categories as gingivitis, periodontitis, and all patients.

There were significant positive correlations between FSH levels and BOP (r=0.303, p=0.029) and FSH levels and PI (r=0.383, p=0.005) in periodontitis patients. However, in gingivitis patients no correlation was observed between FSH levels and any periodontal parameters.

Regarding E2 levels, no correlations were observed between infertility and periodontal parameters in gingivitis and periodontitis patients.

Significant negative correlations between AMH levels and PI were observed both in gingivitis (r = 0.755, p=0.003) and periodontitis patients (r = 0.300, p=0.031).

BOP and PI revealed significant negative correlations with AFC values in gingivitis patients (r=0.615, p=0.025 and r=0.799, p=0.00, respectively) and in periodontitis patients (r=0.349, p=0.011 and r= 0.400, p=0.003, respectively).

When all patients were taken together (n=65), the correlations between periodontal and infertility parameters were like the following:

- FSH levels had significantly positive correlations with all periodontal parameters.
- No significant correlations between periodontal parameters and E2 levels were observed.
- AMH levels had significantly negative correlations with all periodontal parameters except CAL.
- AFC values had significantly negative correlations with all periodontal parameters.

**Table 4.7.** Correlation between clinical periodontal parameters and infertility parameters

| PD Status | | | FSH | E2 | AMH | AFC |
|---|---|---|---|---|---|---|
| **Gingivitis n=13** | **PPD** | Pearson Correlation | -0.479 | -0.206 | -0.321 | -0.421 |
| | | p value | 0.098 | 0.500 | 0.284 | 0.152 |
| | **CAL** | Pearson Correlation | -0.414 | 0.031 | -0.030 | -0.097 |
| | | p value | 0.159 | 0.919 | 0.922 | 0.752 |
| | **BOP** | Pearson Correlation | -0.071 | 0.342 | -0.524 | -0.615 |
| | | p value | 0.817 | 0.253 | 0.066 | **0.025*** |
| | **PI** | Pearson Correlation | 0.259 | 0.284 | -0.755 | -0.799 |
| | | p value | 0.392 | 0.347 | **0.003**** | **0.00**** |
| **Periodontitis (LStIGrB + GStIGrB + GStIIGrB) n=52** | **PPD** | Pearson Correlation | 0.250 | 0.117 | -0.153 | -0.164 |
| | | p value | 0.074 | 0.407 | 0.279 | 0.246 |
| | **CAL** | Pearson Correlation | 0.183 | 0.094 | -0.147 | -0.146 |
| | | p value | 0.193 | 0.506 | 0.297 | 0.303 |
| | **BOP** | Pearson Correlation | 0.303 | 0.102 | -0.184 | -0.349 |
| | | p value | **0.029*** | 0.474 | 0.192 | **0.011*** |
| | **PI** | Pearson Correlation | 0.383 | 0.076 | -0.300 | -0.400 |
| | | p value | **0.005**** | 0.595 | **0.031*** | **0.003**** |
| **All patients n=65** | **PPD** | Pearson Correlation | 0.273 | 0.150 | -0.266 | -0.317 |
| | | p value | **0.028*** | 0.232 | **0.032*** | **0.010*** |
| | **CAL** | Pearson Correlation | 0.258 | 0.160 | -0.226 | -0.279 |
| | | p value | **0.038*** | 0.202 | 0.071 | **0.024*** |
| | **BOP** | Pearson Correlation | 0.327 | 0.170 | -0.356 | -0.492 |
| | | p value | **0.008**** | 0.175 | **0.004**** | **0.000**** |
| | **PI** | Pearson Correlation | 0.409 | 0.135 | -0.471 | -0.550 |
| | | p value | **0.001**** | 0.284 | **0.000**** | **0.000**** |

Pearson Correlation test, *p<0.005, **p<0.001

## 5. DISCUSSION AND CONCLUSION

The link between maternal periodontal infection and female infertility is a new field of research (13, 14). An important question still remains unanswered whether female infertility parameters may be influenced by periodontal inflammation or PD status (197). Since chronic inflammatory PDs are common among adults (36-39) and there is a possible relationship between PDs and pregnancy outcomes (87-94), highlighting the impact of PDs on infertility becomes very relevant considering the high infertility rates all over the world (146).

An extensive list of systemic conditions has a significant negative effect on conception such as unstable diabetes (198), severe renal disease (199), subclinical hypothyroidism (200), uncontrolled celiac disease (201), autoimmune conditions (202), etc. In this study, regarding the patient selection, infertile patients with systemic diseases were excluded to examine the relationship between infertility and PD status without the contribution of any other known disease.

In about half of the infertility cases, infertility is caused by male factors (8). However, male patients with infertility factors were not included in this study since the female infertility parameters were aimed to be associated or correlated with PD status and periodontal parameters.

Endometriosis and PCOS, which are sources of low-grade chronic inflammation and potential causes of infertility (137, 203), are other exclusion criteria of this study. The relationship between PD and endometriosis was explained by a dysregulation in the immune system (137). The link between PCOS and PD is associated with hyperinsulinemia, hyperandrogenism, increased oxidative stress and inflammatory burden (142, 144, 203). Besides, PCOS have an enhancing effect on the periodontally pathogenic bacteria and their association with gingival tissues (143). For excluding selection bias, the women with endometriosis and PCOS at initial recruitment were not included.

All participants were Turkish to eliminate confounders of race in both periodontal and infertility parameters.

Apart from serum FSH, E2 and AMH levels, there are other diagnostic serum markers of infertility such as progesterone, prolactin, luteinizing hormone (LH) and thyroid stimulating hormone (TSH) (148). The utility of assessing progesterone level is limited due to the high false-positive and false-negative rates with associated with the presence or absence of estrogen production (204). Therefore, progesterone level was not evaluated in this study. If there is no clinical evidence of ovulation, evaluation of the prolactin, LH, and TSH levels has been recommended (148). Besides, measurement of prolactin level is beneficial to rule out pituitary tumor, and evaluation of TSH is necessary to rule out hypothyroidism (204). Thus, the levels of LH, prolactin, and TSH were not evaluated since only the patients with clinical evidence of ovulation without thyroid disorders and/or pituitary tumors were taken in this study.

This cross-sectional descriptive study evaluated the characteristics of infertile women attending IVF clinics in terms of age, education level, BMI, smoking habits, oral-hygiene related behaviors, and OHRQoL. The infertility and periodontal parameters, as well as PD status were presented to find out if plaque-induced PDs may be an impact factor in infertility. Possible associations between PD status and infertility parameters together with correlations between periodontal and infertility parameters were assessed before IVF treatment.

Periodontal examinations were performed before the initiation of the IVF cycle, since ovarian stimulation during IVF might turn women more prone to gingival inflammation through hormonal overload (10, 13, 31, 191, 192). Radiographs are integral part of periodontal assessment, which is always performed along with the clinical assessments as an adjunct to determine the periodontal diagnosis (40, 205). In the previous studies investigating the relationship between female infertility and PDs, only PPD or CAL parameters were used to assess PD status without using any radiographs (10, 13, 20, 22, 23). Therefore, these studies should be interpreted with caution, considering the requirements of a correct diagnosis of PDs. In this study, radiographs were taken from each patient to perform the proper diagnostic approach. Besides, this is the first study to investigate the possible relationship between infertility and periodontal parameters and PD status determined by using the 2018 EFP/AAP classification system.

The highest number, 23 out of 65 infertile patients (age range of 24-46 years) attending IVF clinics, appeared in the age category of 31-35 years when the participants were evaluated on a patient basis. However, in line with the age category for infertility in the literature (178), 34 patients were under the age of 36 whereas the rest of them were 36 and above. The highest number of patients, 39 out of 65, were university graduates. There was no uneducated patient confirming the results of studies stating that IVF is preferred by educated people (206). Sixty out of 65 patients revealed BMI values eligible for IVF whereas 5 were fallen into obese category. There were no under-weight patients. Most of the patients, 42 out of 65, were non-smokers. The rest was smoking less than 10 cigarettes per day, 15 of whom expressed less than 5 per day verbally. Most of the patients, 52 out of 65, were brushing their teeth twice a day. However, interproximal cleaning, and mouth rinse consumption were rather infrequent. The above-mentioned descriptive characteristics of patients, except age, did not reveal a statistically significant difference between the different types of PD status as gingivitis, LStIGrB periodontitis, GStIGrB periodontitis, and GStIIGrB periodontitis. The number of ≥ 36 years old patients (n=16) in the GStIIGrB periodontitis group was statistically significant.

Obesity and smoking are possible risk factors considered in the overall life-style influences, influencing ovulation, fallopian tube function, implantation, and miscarriage (154). Hart et al. (9) demonstrated that while factors such as BMI and smoking status which affect female fertility were controlled, the presence of PD still had adverse effects on “time to conception”. Therefore, obese, and smoking patients are included in the assessments of this study.

Monitoring gingival health or inflammation is best documented by BOP as a more objective inflammatory parameter (207-209). Sites without bleeding can be considered as clinically healthy and periodontally stable (40). Therefore, BOP parameter was used to evaluate the gingival inflammation in this study. PPD and CAL parameters used as evidences of gingival health-disease, history of the disease and treatment needs in conjunction with BOP (40). CAL reveals the severity of destroyed and damaged tissue related to the history of periodontitis, while PPD indicates the treatment needs and the complexity of management (48). PI was also recorded since the main etiologic factor of PDs is microbial dental plaque (2, 210), and the link between systemic diseases and PDs has been attributed to periodontal pathogens in the microbial dental plaque biofilm (150).

The results of this study showed that all infertile women presented plaque-induced periodontal diseases. There were no periodontally healthy patients within the study population.

Among the participants, 13 were diagnosed as gingivitis, and the rest revealed different stages and extent of periodontitis, presenting different levels of inflammation and periodontal destruction. Moreover, infertile women presented worsening of PD status as periodontitis according to age, mainly over 35 years old. Since age is a key risk factor for infertility due to various endocrine etiologies and natural elevation of the systemic inflammation (211), the worsening of PD status with age in this particular patient population, may give evidence for a higher risk for infertility when aging is combined with PD presence.

The proposed mechanism of action for PD and infertility link, is the showering of periodontal microorganisms and by products into the circulatory system with local and systemic inflammatory and immune responses (212-215). PD leads to a chronic inflammatory status (216-224) creating an oxidative stress environment which at the end acts as an impact factor on endocrine system decreasing fertility rates (142, 225).

Gingivitis is commonly painless and most patients are unaware of the disease (226). However, periodontitis can lead to tooth loss and disability, which affects chewing function and aesthetics, is the source of social inequality and impairs QoL (4). With the increasing severity and extent of PDs, their influences on OHRQoL increases (5). In this study, OHIP-14 questionnaire was used to assess OHRQoL. The results showed that only "functional limitation" domain of OHIP-14 questionnaire was found statistically significant in GStIIGrB periodontitis patients when compared with the other PD status groups, suggesting the lack of oral health awareness in these patients. Infertility as a concern may have a priority over oral health. Therefore, it is of critical importance to enlighten infertile patients about the relationship of PDs with infertility. Therefore, assessment of the relationship between OHRQoL and PD status in infertile patients are of concern for the enlightenment of these patients.

One of the limitations of this study includes the small number of patients in each PD status groups. This is the reason for why mild and moderate periodontitis patients were merged as well as all patients were taken together during the assessment of

correlations between the infertility and periodontal parameters. Moreover, periodontitis patients revealed only mild to moderate periodontitis stages as another limitation.

Despite the aforementioned limitations, significant associations with infertility parameters and PD status were found in this study. Both AMH levels and AFC values were significantly lower in GStIIGrB periodontitis group compared to gingivitis group. Statistically significant correlations were also observed between periodontal and infertility parameters. Regarding gingivitis patients, BOP and PI revealed negative correlations with AFC values. Furthermore, statistically significant negative correlations were found between AMH levels and PI in gingivitis patients. Regarding periodontitis patients, significant positive correlations between FSH levels and both PI and BOP were observed. Furthermore, a significant negative correlation was found between AMH levels and PI. AFC, on the other hand, presented a negative correlation with BOP and PI. CAL and PPD as periodontal parameters did not show any correlation with the infertility parameters. When it comes to all patients, FSH was significantly and positively correlated with all periodontal parameters. AMH was significantly and negatively correlated with all periodontal parameters except CAL. AFC was significantly and negatively correlated with all periodontal parameters. Thus, significant correlations were indeed found between the inflammation-related periodontal parameters as BOP and PI and the different parameters of infertility. E2 was the only infertility parameter that had no significant correlation with any of the periodontal parameters.

The findings presented here may provide a proof of concept for the investigated interaction of two systemically distinct conditions. The AFC findings specifically pointed out a possible association between periodontal parameters and diminished AFC values.

This is the first and only study assessing the association and correlation of PD status and periodontal parameters with infertility parameters prior to IVF treatment. Therefore, it was not possible to discuss our results with the existing studies in the literature.

As mentioned before, there is robust evidence that the PDs and systemic diseases are associated through the inflammation pathway as the common theme (75, 131, 134, 136). The entire infertile patient population of this study revealing periodontal inflammation may be a critical finding for the importance of gingival inflammation on

infertility. Only individuals with GStIIGrB periodontitis in the study population had significantly lower AMH and AFC parameters. Thus, it has been observed that infertile individuals demonstrated negative effects on infertility parameters with the progressing PD status.

Within the limitations of this study, present findings encourage that larger study population should further be undertaken to confirm the impact of PDs on infertility and to determine the effect of PD on IVF treatment, achievement of pregnancy as well as birth outcomes. With the proven associations and negative correlations of PD status/periodontal parameters with infertility parameters in women seeking IVF treatment, periodontal consultations might be a critical importance for prenatal care and possibly increase fertility success.

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# 7. APPENDICES

## 7.1. Ethical Approval

T.C. YEDİTEPE ÜNİVERSİTESİ

**Sayı :** 37068608-6100-15- 2129
**Konu:** Klinik Araştırmalar
Etik Kurul Başvurusu hk.

**22/04/2021**

İlgili Makama (Ogül Leman Tunar/Naz Kurt)

Yeditepe Üniversitesi Diş Fakültesi Periodontoloji AD. Prof. Dr. Bahar Eren Kuru'nun sorumlu araştırmacı olduğu, Dr. Öğr. Üyesi Ogül Leman Tunar ve Dt. Naz Kurt'un yardımcı sorumlu araştırmacı olduğu, Tıp Fakültesi Kadın Hastalıkları ve Doğum AD. Prof. Dr. Erkut Attar'ın yardımcı araştırmacı olduğu **"İn Vito Fertilizasyon Tedavisi Gören Hastalarda Periodontal Durum ve İnfertilite Parametreleri Arasındaki İlişkinin Değerlendirilmesi: Kesitsel Bir Çalışma"** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası**(2154)** kayıtlı Numaralı KAEK Başvuru Dosyası, Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **21.04.2021** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isim belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir **(KAEK Karar No: 1422)**

Prof. Dr. Hasan AYDIN

Yeditepe Üniversitesi
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## 7.2. Informed Consent Form

| T.C. YEDİTEPE ÜNİVERSİTESİ | KLİNİK ARAŞTIRMALAR ETİK KURULU<br><br>BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU | |
|---|---|---|

| **Hastanın veya yerine onam verecek kişinin okuma, anlama, konuşma, dil sorunu mevcut mu?**<br>Evet Hayır<br>Cevabınız EVET ise Hasta İlişkileri Sorumlusu ile iletişim kurunuz. | **Tercüman gerektiyse;**<br>Tercümanın adı _____<br>İmza _____<br>Tarih _____ |
|---|---|

**Sayın Hastamız,**

- Bu belge bilgilendirilme ve aydınlatılmış onam haklarınızdan yararlanabilmenizi amaçlamaktadır.
- Size gerçekleştirilebilecek klinik araştırmalar amaçlı girişimler konusunda, tüm seçenekler ile bu girişimlerin yarar ve muhtemel zararları konusunda anlayabileceğiniz şekilde **bilgi alma hakkınız ve bir kopyasını isteme hakkınız** vardır.
- Yasal ve tıbbi zorunluluk taşıyan durumlar dışında **bilgilendirmeyi reddedebilirsiniz**. Yazılı bildirmek koşulu ile bilgi almama veya yerinize güvendiğiniz bir kimsenin bilgilendirilmesini talep etme hakkına sahipsiniz.
- Klinik araştırmalara katılım konusunda bilgilendirildikten sonra bunu kabul edebilirsiniz. Ya da **karar verebilmek için uygun zaman talep edebilirsiniz.**
- Hayatınız veya hayati organlarınız tehlikede olmadığı sürece onamınızı (yazılı talep etme koşulu ile) **dilediğiniz zaman geri alabilir** ya da önceden kabul etmediğiniz herhangi bir tanı/tedavi amaçlı girişimi **tekrar talep edebilirsiniz**.
- Hastanemizde verilen hizmetleri **Hastane Tanıtım Broşürü**nden edinebilirsiniz. Ayrıca Hastanemiz personeli hakkında http://www.yeditepehastanesi.com.tr/ web sayfamızdan daha detaylı bilgilere ulaşabilirsiniz.

Burada belirtilenlerden başka sorularınız varsa bunları yanıtlamak görevimizdir.

**TANIMLAMA**

**Protokol numarası: 397**

**Araştırmanın Adı: İn Vitro Fertilizasyon Tedavisi Gören Hastalarda Periodontal Durum ve İnfertilite Parametreleri Arasındaki İlişkinin Değerlendirilmesi: Kesitsel Bir Çalışma**

***Sorumlu Araştırmacının Adı:*** *Prof. Dr. Bahar KURU*

***Yardımcı Araştırmacının Adı:*** *Dr. Öğr. Üyesi Ogül Leman TUNAR*

***Yardımcı Araştırmacının Adı:*** *Dt. Naz Kurt*

**Bu Araştırmanın Konusu ve Amacı:**

Bu katıldığınız çalışma bilimsel bir araştırma olup, araştırmanın adı "İn Vitro Fertilizasyon Tedavisi Gören Hastalarda Periodontal Durum ve İnfertilite Parametreleri Arasındaki İlişkinin Değerlendirilmesi: Kesitsel Bir Çalışma" dır.

Periodontal hastalık, çok sayıda sistemik hastalık için potansiyel risk faktörü olarak düşünülmektedir. Periodontitisin gebeliği sınırlayan, modifiye edilebilen bir risk faktörü olabileceğini ve periodontal hastalığın doğurganlığı azaltabileceğini varsayan çalışmalar vardır. Bu çalışma, sizin Yeditepe Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, İn Vitro Fertilizasyon Kliniğindeki muayeneniz sırasında bakılan infertilite parametreleriniz ve infertilite nedeniniz ile periodontal durumunuz arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır. Ayrıca yaş, eğitim seviyesi, boy ve kilo gibi sosyodemografik faktörlerin, sigara gibi yaşam tarzı faktörlerinin ve oral hijyen alışkanlıklarınızın infertilite ve periodontal durum üzerindeki etkisini araştırmak ve ağız sağlığına bağlı yaşam kalitenizi ölçmek amaçlanmaktadır.

Hamile kalım öncesinde kişinin periodontal olarak sağlıklı olması son derece önemlidir. İnfertil kadınlardaki hamile kalma oranları sadece periodontal sağlığın iyileştirilmesiyle arttırılabilir.

**Araştırmaya Katılımcı Sayısı**

2021 yılının ikinci çeyreğinden 2022 yılının ikinci çeyreğine kadar Yeditepe Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, İn Vitro Fertilizasyon Kliniğine başvuran infertil kadın bireyler çalışmaya dahil edilecektir. Çalışmamızda, kliniğimize başvuran hastalardan çalışmaya dahil edilme kriterine uyanlar seçilecektir.

**Bu çalışmaya katılmalı mıyım?**

Bu çalışmada yer alıp almamak tamamen size bağlıdır. Eğer katılmaya karar verirseniz bu yazılı bilgilendirilmiş olur formu imzalanmak için size verilecektir. Şu anda bu formu imzalasanız bile muayene süresince seans içerisinde herhangi bir zamanda bir neden göstermeksizin çalışmayı bırakmakta özgürsünüz.

**Süresi**

Periodontoloji Anabilim dalına yönlendirilen her katılımcı bir seans içerisinde periodontal durumları açısından değerlendirilecektir. Çalışmaya devamlılık gerektiren bir süreç yoktur.

**Bu çalışmaya katılırsam beni neler bekliyor?**

**İzlenecek Yöntem / Yöntemler**

IVF Kliniğinden Periodontoloji Anabilim Dalına yönlendirilen her katılımcı için çalışmaya dahil olma süreci sadece bir muayene/teşhis seansı olacaktır. Seansta ağız bakımınız, dişleriniz ve dişetlerinizin durumunu kaydetmek için periodontal muayene takımının içinde bulunan ve rutin muayenede kullanılan periodontal sond dediğimiz bir aletle ağzınızda bazı ölçümler yapacağız ve bu ölçümleri kaydedip periodontal durumunuzu (periodontal olarak sağlıklı, gingivitis veya periodontitis hastası) değerlendireceğiz. Ayrıca teşhis amaçlı panoramik radyografi alacağız.

Yaşınızı, eğitim seviyenizi, boyunuzu, kilonuzu, sigara tüketiminizi, oral hijyen alışkanlıklarınızı, genel sağlık durumunuzu, kullandığınız ilaçları, geçirdiğiniz ameliyatları not edeceğiz.

Dişeti hastalıklarının nedeni olan bakteri plağı, bakteri plağından korunma yöntemleri, diş fırçalama yöntemi, diş ipi ve/veya arayüz fırçası kullanımı öğretilecektir.

Çalışmaya katılan her birey için aynı yöntem izlenecektir.

**Çalışmanın riskleri ve rahatsızlıkları nelerdir, göreceğim olası bir zarar durumunda ne yapılacak?**

Herhangi bir girişimsel müdahelede bulunulmayacaktır. Çalışma sonrasında olası bir risk beklenmemektedir. Çalışmamızdan dolayı herhangi bir zarar veya yan etki görmeniz durumunda her türlü tıbbi müdahale yapılacaktır ve konu ile ilgili harcamalar tarafımızdan karşılanacaktır.

**Risk / rahatsızlık durumlarında yapılması gerekenler**

Çalışma sonrasında olası bir risk beklenmemektedir ancak herhangi bir olası sorun ve rahatsızlıkta aşağıda bilgileri verilen araştırmacıya ulaşılınmalıdır.

**Aşağıdaki özel durumlara ait katılımcı var mı?**

**Evet*** **Hayır**

| | **Evet** | **Hayır** |
|---|---|---|
| **Çocuk** | | **X** |
| **Mahkum** | | **X** |
| **Gebe** | | **X** |
| **Sosyoekonomik eğitimi olarak yetersiz** | | **X** |
| **Mental yetersizlik** | | **X** |

*Ancak kısıtlılık durumunda; gönüllüler yönünden araştırmadan doğrudan fayda sağlanacağı umuluyor ve araştırma gönüllü sağlığı açısından öngörülebilir ciddi bir risk taşımıyor ise, usulüne uygun bir şekilde alınmış bilgilendirilmiş gönüllü olur formu ile birlikte ilgili etik kurulun onayı ve Bakanlık izni alınmak suretiyle araştırmaya izin verilebilir.

**Alternatif Tedavi Veya Girişimler**

Sizlere herhangi bir girişimsel müdahelede ve tedavide bulunulmayacaktır. Çalışma tanı amaçlı yapılacak olan girişimsel olmayan bir çalışmadır.

**Ne yapmam gerekiyor, sorumluluklarım nelerdir?**

Sizlere herhangi bir girişimsel müdahelede bulunulmayacaktır. Çalışma ile ilgili herhangi bir sorumluluğunuz yoktur. Ağız hijyeninize dikkat etmeniz hem kendi sağlığınız hem de olası hamilelik süreciniz ve bebeğin sağlığı açısından önemlidir ve önerilmektedir.

**Araştırma Sonunda Beklenen Fayda**

Hamile kalım süreci öncesi ve sonrasında kişinin periodontal olarak sağlıklı olması son derece önemlidir.
Çalışmaya katılmanız durumunda periodontal durumunuz hakkında bilgi sahibi olacak ve ağız hijyen eğitimi alacaksınız. Herhangi bir ücret ödemeniz gerekmemektedir.

**Çalışma hakkında yeni bilgiler elde edilirse ne olacak?**

Çalışmamız her katılımcı için birer seans sürecek olan bir çalışmadır. Çalışmaya katılım devamlılığı olmadığından bir çalışma süreci yoktur.

**Araştırmadan kendi isteğim dışında çıkmam gerekebilir mi?**

Çalışmamız katılım devamlılığı olan bir çalışma değildir. Her katılımcı bir seans içerisinde değerlendirilecektir.

**Bu çalışmaya katılmamın maliyeti nedir?**

Çalışmaya katılmakla parasal yük altına girmeyeceksiniz ve size de herhangi bir ödeme yapılmayacaktır.

**Kişisel bilgilerim nasıl kullanılacak?**

Çalışma doktorunuz kişisel bilgilerinizi, araştırmayı ve istatiksel analizleri yürütmek için kullanacaktır. Çalışmanın sonunda, bu bilgiler hakkında bilgi istemeye hakkınız vardır. Çalışma sonuçları çalışma bitiminde tıbbi literatürde yayınlanabilecektir ancak kimliğiniz açıklanmayacaktır.

İzleyiciler, yoklama yapan kişiler, Etik Kurul, Sağlık Bakanlığı ve diğer ilgili sağlık otoriteleri orijinal tıbbi kayıtlarınıza doğrudan erişebilir. Bu yazılı bilgilendirilmiş gönüllü olur formunu

imzalayarak yalnızca adı geçen kişi ve kurumlara erişim izni vermiş olacaksınız. Ancak kimlik bilgileriniz gizli tutulacak, kamuoyuna açıklanamayacak; araştırma sonuçlarının yayımlanması halinde dahi kimliğiniz gizli kalacaktır.

**Araştırmadan çekilirsem ne olur?**

Çalışmamız bir seansı kapsayan bir çalışmadır. Çalışmaya katılım devamlılığı dolayısıyla bir çalışma süreci yoktur. Ancak muayene seansında alınan verilerinizin araştırmada kullanılmasını istedemediğiniz takdirde herhangi bir cezaya veya yaptırıma maruz kalmaksızın araştırmadan çekilebilirsiniz.

**Daha fazla bilgi, yardım ve iletişim için kime başvurabilirim?**

Çalışma ile ilgili bir sorununuz olduğunda ya da çalışma ile ilgili ek bilgiye gereksiniminiz olduğunuzda aşağıdaki kişi ile lütfen iletişime geçiniz.

ADI : Naz Kurt
TELEFON :

***(Katılımcının/Hastanın Beyanı)***

Bana yukarıda konusu ve amacı belirtilen araştırma ile ilgili yazılı ve sözlü açıklama Yeditepe Üniversitesi Periodontoloji Anabilim dalında, Dt. Naz Kurt tarafından yapıldı. Bilgilendirilmiş Gönüllü Olur Formu'ndaki tüm açıklamaları okudum. Bana aktarılan bilgiler ışığında ilgili metni okuduktan sonra böyle bir araştırmaya "katılımcı" olarak davet edildim.

Araştırmaya katılmam konusunda zorlayıcı bir davranışla karşılaşmış değilim. Araştırmaya gönüllü olarak kendi rızamla katılıyorum ve istediğim zaman gerekçeli veya gerekçesiz olarak araştırmadan ayrılabileceğimi biliyorum. Eğer katılmayı reddedersem, bu durumun tıbbi bakımıma ve hekim ile olan ilişkime herhangi bir zarar getirmeyeceğini de biliyorum.
Araştırma için yapılacak harcamalarla ilgili herhangi bir parasal sorumluluk altına girmiyorum. Bana da bir ödeme yapılmayacaktır.

İster doğrudan, ister dolaylı olsun araştırma uygulamasından kaynaklanan nedenlerle meydana gelebilecek herhangi bir sağlık sorunumun ortaya çıkması halinde, her türlü tıbbi müdahalenin sağlanacağı konusunda gerekli güvence verildi.

Çalışmadan elde edilen sonuçların kullanılmasını kısıtlamamayı, yayın, rapor ve benzeri bilimsel dokümanlarda kullanılmasını kabul ediyorum.
Araştırma ile ilgili herhangi bir sorunum/ sorum olduğu durumda günün herhangi bir saatinde

| T.C. YEDİTEPE ÜNİVERSİTESİ | KLİNİK ARAŞTIRMALAR ETİK KURULU<br><br>BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU | |
|---|---|---|

Dt. Naz Kurt'u, Yeditepe Üniversitesi Diş Hekimliği Fakültesi Periodontoloji A.D veya numaralı telefondan arayabileceğimi biliyorum.

Bana yapılan tüm açıklamaları ayrıntılarıyla anlamış bulunmaktayım. Bu koşullarla söz konusu klinik araştırmaya kendi rızamla, hiçbir baskı ve zorlama olmaksızın, gönüllülük içerisinde katılmayı kabul ediyorum. Bilgilendirilmiş gönüllü olur formundaki tüm açıklamaları okudum. Bana yukarıda konusu ve amacı belirtilen araştırma ile ilgili yazılı ve sözlü açıklama aşağıda adı belirtilen hekim tarafından yapıldı.

Söz konusu araştırmaya, hiçbir baskı ve zorlama olmaksızın kendi rızamla katılmayı kabul ediyorum. İmzalı bu form kağıdının bir kopyası bana verilecektir.

**Gönüllünün;**

Adı / Soyadı:

İmzası:

Tarih:

Telefon Numarası:

**Araştırmayı Yürüten ve Araştırma Hakkında Bilgilendirmeyi Yapan Kişinin;**

Adı / Soyadı:

İmzası:

Tarih:

Telefon Numarası:

**Olur İşlemine Tanık Olan Kişinin;**

Adı / Soyadı:

İmzası:

Tarih:

**Gerekiyorsa Yasal Temsilcinin;**

Adı / Soyadı:

İmzası:

Tarih:

## 7.3. Self-reported Questionnaire

**Ad/ Soyad:**

**Yaş:**

**Boy:** **Kilo:**

**Eğitim Durumu:** İlköğretim-Ortaöğretim / Lise / Üniversite / Yüksek lisans-Doktora

**Diş Fırçalama Sıklığı**: Hiç / Günde 1 kez / Günde 2 kez / Düzensiz

**Arayüz Temizliği:** Hiç / Günde 1 kez / Günde 2 kez / Düzensiz
**(Diş İpi-Arayüz Fırçası)**

**Gargara Kullanımı:** Hayır / Evet

**Sigara:** Kullanmıyorum / Günde 10 taneden az / Günde 10 tane ve üstü / İçmeyi bıraktım

## 7.4. Oral Health Impact Profile-14 (OHIP-14) Questionnaire

**OHIP-14 ANKET FORMU**

1. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile herhangi bir kelimeyi telaffuz etmekte sorununuz oldu mu?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

2. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile tat alma hissinizin bozulduğunu hissediyor musunuz?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

3. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile ağzınızda ağrılı bir durum yaşadınız mı?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

4. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile yemek yemeyi rahatsız edici buldunuz mu?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

5. Daha önceden, dişleriniz, ağzınız veya protezlerinizle ilgili bilinç ve bilgiye sahip miydiniz?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

6. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile gerginlik hissettiniz mi?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

7. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile diyetinizin tatmin edici olmadığı oldu mu?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

8. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile yemeğinizi yarıda bırakmak zorunda kaldınız mı?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

9. Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile gevşemede zorlandığınız oldu mu?

   0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

**10.** Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile utandığınız bir durum oldu mu?

0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

**11.** Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile diğer insanlara az da olsa asabi davrandığınız oldu mu?

0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

**12.** Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile her zaman yaptığınız işinizi yapmada herhangi bir zorluk yaşadınız mı?

0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

**13.** Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile genelde hayatın daha az tatmin edici olduğu hissine kapıldınız mı?

0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

**14.** Dişleriniz, ağzınız veya protezleriniz ile ilgili problemler nedeni ile fonksiyonlarınızı tümüyle yapamayacak duruma geldiniz mi?

0= Hiçbir zaman 1=Çok Az 2=Ara Sıra 3=Oldukça Sık 4=Sık Sık

# 8. CURRICULUM VITAE

**Personal Informations**

| | | | |
|---|---|---|---|
| **Name** | Naz | **Surname** | Kurt |
| **Place of Birth** | | **Date of Birth** | |
| **Nationality** | | **TR ID Number** | |
| **E-mail** | | **Phone number** | |

**Education**

| **Degree** | **Department** | **The name of the Institution Graduated From** | **Graduation year** |
|---|---|---|---|
| **Doctorate** | Periodontology | Yeditepe University | 2022 |
| **University** | Dentistry | Yeditepe University | 2018 |
| **High school** | - | Bursa Anatolian High School | 2013 |

| **Languages** | **Grades** |
|---|---|
| English | YÖKDİL: 91.25 |

**Computer Skills**

| **Program** | **Level** |
|---|---|
| Microsoft Word | Excellent |
| Microsoft PowerPoint | Excellent |
| Microsoft Excel | Good |
| SPSS Statistics | Basic |

**Scientific works**

**Proceedings presented in international scientific meetings and published in proceedings book.**

| |
|---|
| Periodontally Accelerated Osteogenic Orthodontics with Piezosurgery: A Case Report. International 2nd Dental Oral Infections (2.Doinf) and 1st Oral Microbiota Congress |

**Others (Projects / Certificates / Rewards)**

| |
|---|
| International 4th YUDBAT Congress, Best Oral Presentation Award. In vitro Comparison of the Plaque Removal Efficacy of Two Different Interdental Cleaning Devices. 2017, Istanbul, Turkiye. |
| Journal of Clinical Periodontology Digest Issue number 78, published in October 2020, a summary of the article 'Periodontal regeneration versus extraction and dental implant or prosthetic replacement of teeth severely compromised by attachment loss to the apex: A randomized controlled clinical trial reporting 10-year outcomes, survival analysis and mean cumulative cost of recurrence' |
| Journal of Clinical Periodontology Digest Issue number 95, published in February 2021, a summary of 'Two short implants versus one short implant with a cantilever: 5-Year results of a randomized clinical trial' |