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PATHOPHYSIOLOGICAL BASES OF THE RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND FEMALE FERTILITY

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Abstract: Female infertility is a multifactorial condition affecting approximately 17.5% of the world's population. Recently, periodontitis, a chronic inflammatory disease resulting from oral biofilm dysbiosis, has been identified as a critical systemic risk factor. The translocation of pathogens such as *Porphyromonas gingivalis (Pg)* and the release of pro-inflammatory cytokines (TNF-α, IL-1β) into the bloodstream establish a mechanistic link that compromises the homeostasis of the female reproductive system. To elucidate the immunoinflammatory and molecular mechanisms by which periodontal disease interferes with female fertility, emphasizing the impacts on ovarian physiology and endometrial receptivity. The study is based on a critical analysis of scientific evidence, integrating epidemiological data from the WHO, international classifications of periodontal diseases, and findings from multicenter clinical studies. Furthermore, it utilizes the support of animal experimental models for the analysis of histomorphometric and molecular variables (follicular reserve and hormone receptor expression) that could not be detailed in humans due to ethical limitations. In the reviewed articles, evidence demonstrates that periodontitis significantly increases the time to conception (TTC) from 5.0 to 7.1 months. In addition, at the ovarian level, the inflammatory load induces oxidative stress and mitochondrial dysfunction, promoting follicular apoptosis and oocyte DNA damage. In the uterus, *Pg* infection and the increase in matrix metalloproteinases (MMP-8) cause an abnormal upregulation of estrogen (ER-α) and progesterone (PR) receptors, preventing decidualization and embryo implantation. Additionally, periodontal comorbidity acts as an inflammatory amplifier in patients with PCOS and endometriosis, exacerbating the severity of these conditions. Periodontitis acts as an aggressive systemic modulator of reproductive function. The integration between the periodontium and the reproductive axis is sustained by an inflammatory-oxidative cascade that impairs both oocyte quality and the endometrial microenvironment. Therefore, periodontal health must be considered an inseparable pillar of family planning, making dental screening essential in assisted reproduction protocols to optimize the chances of conceptual success.

Keywords: Female infertility; Periodontitis; Oxidative stress; Endometrium; Ovarian reserve; Systemic health.

Introduction

Female infertility is clinically defined as the inability to achieve pregnancy after 12 months of regular and unprotected sexual intercourse in women under 35 years of age, or after 6 months in women aged 35 or older (ASRM, 2013). This condition transcends the biological sphere, establishing itself as a global public health issue affecting approximately 17.5% of the adult population (WHO, 2023). The etiology of infertility is multifactorial, encompassing genetic, hormonal, anatomical, immunological, and psychosocial determinants (Crosignani et al., 2009).

In this context, periodontitis, a chronic inflammatory disease that affects the supporting tissues of the teeth, has been increasingly associated with systemic health and female fertility. The underlying mechanisms linking periodontal disease to systemic health include chronic inflammation and immune system dysregulation. The pathology is currently understood as a state

of persistent immunological imbalance. The disruption of the gingival barrier facilitates the translocation of pathogens and their byproducts into the bloodstream, triggering a low-grade systemic inflammatory cascade. This condition establishes a mechanistic link with several non-communicable diseases, such as diabetes mellitus and cardiovascular disorders, consolidating periodontitis as a significant risk factor for the instability of global organic homeostasis (Hasan et al., 2025).

The impact of this inflammatory load on the female reproductive axis is primarily mediated by the oxidative stress cascade. The dissemination of pro-inflammatory cytokines and the systemic increase in reactive oxygen species (ROS) find an integrating center of cellular damage in the ovarian mitochondria (Xu et al., 2025). Mitochondrial dysfunction induced by chronic inflammatory stimuli compromises oocyte quality by promoting mitochondrial DNA mutations and meiotic spindle instabilities. This redox imbalance extends to the uterus and endometrium, where persistent inflammation can alter endometrial receptivity and impair the nidation process, creating a hostile microenvironment for early embryonic development (Dekel et al., 2010; Xu et al., 2025).

Clinical evidence suggests that this inflammatory and oxidative dysregulation can exacerbate the pathogenesis of conditions such as Polycystic Ovary Syndrome (PCOS) and Endometriosis, both characterized by a persistent systemic inflammatory profile. Studies demonstrate a positive correlation between the severity of periodontitis and the worsening of symptoms in these pathologies, suggesting that oral health directly influences the severity of the reproductive condition (Wang et al., 2023; Zhou et al., 2023). Recently, animal model studies have deepened this understanding by demonstrating that infection by *Porphyromonas gingivalis* (*Pg*) induces uterine hypertrophy and an abnormal upregulation of estrogen α (ER-α) and progesterone (PR) receptors, resulting in a lower number of births and nidation failures (Kamei-Nagata et al., 2025).

Despite the growing body of evidence, a significant gap remains in interdisciplinary care, as oral health is frequently neglected in infertility investigation protocols. The vulnerability lies in the fact that asymptomatic oral inflammatory processes can sabotage reproductive interventions without being diagnosed, highlighting the urgent need to integrate periodontal care into family planning. In this scenario, the use of animal experimental models becomes imperative, as it allows for the investigation of the chronology of follicular and uterine degradation under inflammatory stress in a controlled manner.

Given the ethical complexity of investigating such mechanisms in humans, the use of animal models is fundamental. These models allow for rigorous control of variables and detailed histomorphometric analysis of ovarian and uterine structures, enabling an understanding of how induced periodontitis impacts follicular reserve and reproductive functionality at molecular and tissue levels. Such models enable the analysis of mechanistic variables that, due to ethical and methodological limitations, could not be detailed in clinical studies with humans, conferring upon this dissertation a fundamental role in understanding the reproductive pathophysiology associated with periodontitis (Sá et al., 2025).

Thus, the present chapter aims to highlight the immunoinflammatory and molec-

ular mechanisms by which periodontal disease compromises female fertility, focusing on the ovarian and endometrial impact. It seeks to clarify the importance of preserving periodontal health as an essential adjuvant strategy for maintaining the homeostasis of the reproductive system, providing insights for an integrated clinical approach aimed at protecting the follicular reserve and optimizing the uterine environment for successful conception.

Pathophysiology of Periodontal Disease

According to the classification of the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (2017), periodontal pathologies are primarily divided into gingivitis and periodontitis. While gingivitis represents a reversible inflammatory response, its therapeutic neglect culminates in progressive degenerative changes in the supporting tissues.

In individuals with a healthy periodontium and regular oral hygiene habits, an eubiotic biofilm is observed, characterized by its structural immaturity and constant renewal. This condition prevents the establishment of pathogenic bacterial communities and maintains a microbial environment compatible with periodontal health. In these cases, Gram-positive cocci and bacilli predominate, especially streptococci, along with representatives of the so-called yellow, blue, green, and purple bacterial complexes, whose presence is associated with a stable and non-inflammatory oral ecosystem (Pérez-Chaparro et al., 2014).

This balance, however, can be compromised through neglect in oral hygiene care. The reduction in the mechanical removal of

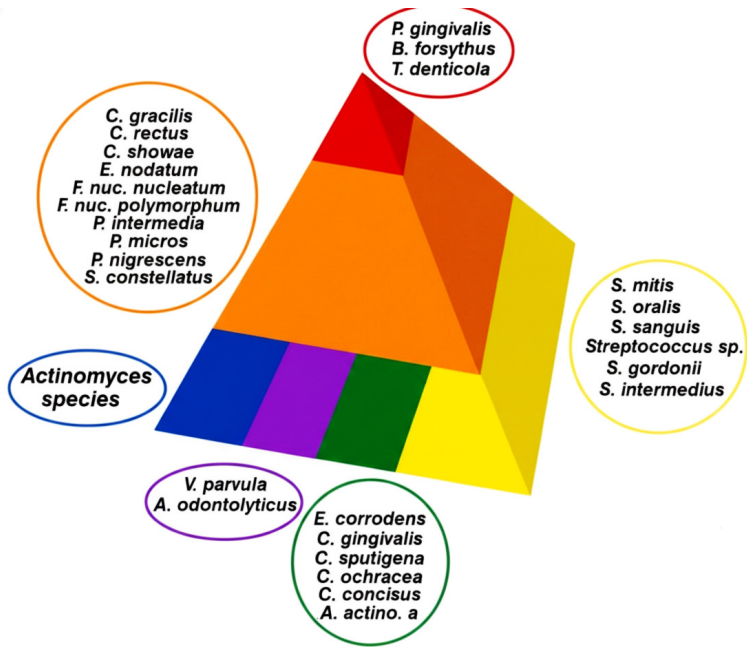

Figure 1: Classification of periodontal microbial complexes adapted from Socransky et al. (1998), highlighting the bacterial distribution in chromatic complexes according to their correlation with periodontal health and periodontitis severity.

the biofilm favors its maturation and colonization by microorganisms with greater pathogenic potential that belong to the "Red Complex," such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (Figure 1), characterizing a process of dysbiosis (Socransky et al., 1998; Carrizales-Sepúlveda et al., 2018). Therefore, periodontitis can be understood as a clinical manifestation of an ecological imbalance in the subgingival biofilm (Van Dyke et al., 2020).

Bacterial colonization begins in the cervical regions of the teeth, where the dentogingival plaque provides a microenvironment conducive to the proliferation and protection of these microorganisms, even against topical antimicrobial agents. Bacterial adhesion to oral surfaces and host cells occurs through specific structures, such as fimbriae and LPS molecules, which function as adhesins and enable interaction with cellular receptors. This interaction not only favors the persistence of pathogens in the oral environment but also triggers host immune responses (Socransky et al., 1998; Carrizales-Sepúlveda et al., 2018).

The presence of periodontal pathogens in the oral cavity, through their virulence factors, promotes the activation of various immune system cells, including T and B lymphocytes, macrophages, and neutrophils (Yucel-Lindberg; Båge, 2013). These cells represent the initial line of defense, being rapidly recruited to the site of infection (Valerio; Kirkwood, 2018), where they initiate the production of pro-inflammatory cytokines to eliminate pathogenic microorganisms and enhance the host's immune response (Mantovani et al., 2019).

As a result of this immune activation, there is a release of inflammatory mediators, such as TNF-α, IL-1β, IL-8, and prostaglan-

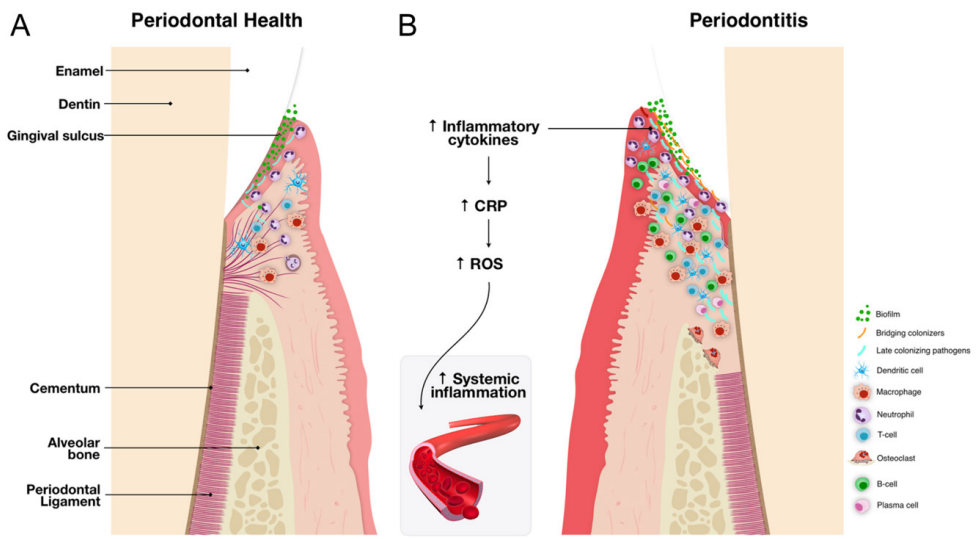

Figure 2: Illustrative scheme of the pathogenesis of periodontitis, showing the activation of the inflammatory response induced by the subgingival biofilm, the release of pro-inflammatory cytokines, and the mechanisms involved in alveolar bone resorption. Adapted from Machado et al. (2020).

din E2 (PGE2) (Figure 2), which exert direct effects on the destruction of periodontal tissues (Garlet et al., 2010). Furthermore, this process stimulates the production of matrix metalloproteinases (MMPs), enzymes responsible for the degradation of the collagen fibers that support the periodontium (Pan et al., 2019).

Among these cytokines, IL-1, IL-8, and TNF-α play an important role in the continuous recruitment of neutrophils to the inflammatory site, perpetuating local inflammation. IL-1, in particular, also induces the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL) in osteoblasts and T-helper lymphocytes, promoting osteoclast differentiation and favoring the process of alveolar bone resorption (Pan et al., 2019).

From a histological perspective, periodontal inflammation leads to the destruction of the bone crest in the coronary region, the degradation of periodontal ligament fibers, and the apical migration of the junctional epithelium from the cementoenamel junction. The inflammatory process also spreads to the tissues adjacent to the periodontal pocket, worsening tissue damage (Kinane et al., 2017).

Systemic Impact of Periodontitis on Ovarian Physiology

Periodontitis, due to its systemic inflammatory nature, exerts an impact that extends beyond the limits of the oral cavity, influencing distant organic structures. The progression of this disease is closely associated with the release of pro-inflammatory mediators and reactive oxygen species (ROS) which, upon reaching the bloodstream, destabilize systemic homeostasis (Pouliou et al., 2024). In the periodontium, this condition acts as a catalyst for the destruction of supporting tissues, while at the cellular level, it promotes the degradation of proteins, nucleic acids, and membrane lipids (Almerich-Silla et al., 2015).

To counter this aggression, the organism mobilizes a complex antioxidant arsenal, including the enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Novakovic et al., 2014). However, when the inflammatory load is persistent, as in chronic periodontitis, this redox balance is violated, generating negative repercussions in the ovarian microenvironment (James et al., 2023). In this scenario, mitochondria act as an integrating center that connects oxidative stress to cellular aging. As elucidated by Xu et al. (2025), the mitochondrial genome (mtDNA) is significantly more vulnerable to oxidative attack than nuclear DNA, both due to its proximity to the respiratory chain and the absence of protective histones.

This vulnerability is exacerbated by the fact that ROS can inhibit the activity of DNA polymerase gamma (POLG), the primary enzyme for mtDNA replication and repair. Under oxidative stress, the efficiency of this enzyme can be reduced by up to 50%, resulting in the accumulation of mutations, such as the formation of 8-oxo-guanine, and the progressive depletion of mitochondrial content (Xu et al., 2025). This ovarian energetic collapse triggers the intrinsic apoptosis pathway (Figure 3) via the release of cytochrome c (Barbalho et al., 2024).

Interestingly, ROS exhibit an ambivalent character in fertility; at controlled levels, they function as essential messengers for meiosis and ovulation (Ribas et al., 2022). However, in excess, they become pathogenic

mediators associated with conditions such as endometriosis and polycystic ovary syndrome (Weng et al., 2023). Oocyte vulnerability is intensified by ovarian senescence, as the long meiotic arrest increases exposure to accumulated damage (Wu et al., 2022). Xu et al. (2025) reinforce that this mitochondrial deterioration is a primary determinant of premature cellular aging, inducing instabilities in the meiotic spindle and failures in cytoskeleton dynamics (Zhang et al., 2018; Xu et al., 2025). Such alterations increase the incidence of chromosomal segregation errors, culminating in a sharp decline in oocyte competence and female reproductive efficacy (Yang et al., 2020).

In view of this, we highlight that cytokines resulting from the periodontitis process, as well as hormonal changes, are involved in the death of ovarian follicles starting from the secondary follicle stage (Fraser et al., 2006).

Molecular Mechanisms of Periodontal Disease and Clinical Repercussions on Human Fertility

Female subfertility has a multifactorial etiology, classically associated with advancing chronological age, high body mass index (BMI), and deleterious lifestyle habits. However, recent investigations have positioned periodontal health as an important determinant of time to conception (TTC). Evidence from the multicenter SMILE study, analyzed by Hart et al. (2012), demonstrates that Periodontal Disease (PD) exerts a deleterious influence on the speed of spontaneous conception. Women diagnosed with the pathology presented a mean TTC of 7.1 months, in contrast to the 5.0 months observed in healthy individuals (P=0.019). The clinical relevance of this condition is reinforced by its higher prevalence (34.9%) in the group that exceeded the 12-month threshold to conceive, suggesting that oral

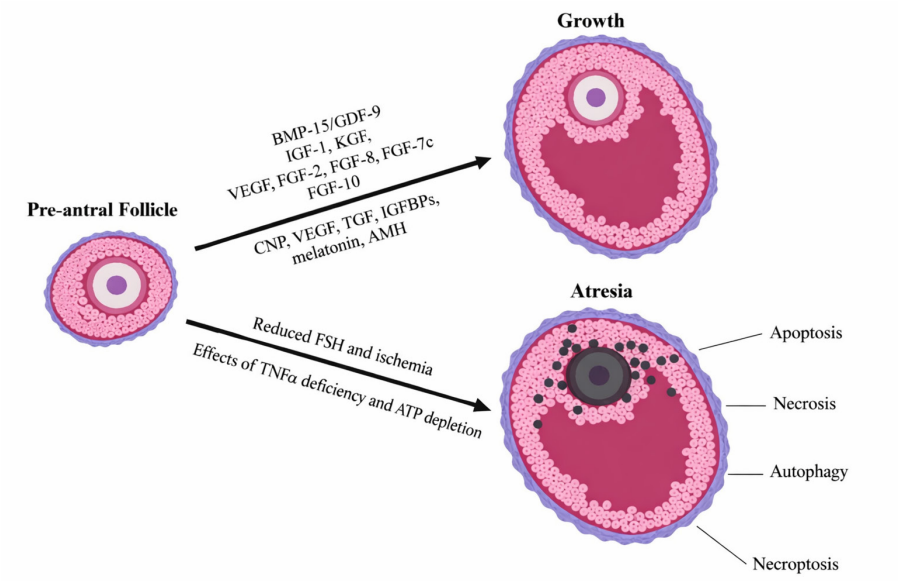

Figure 3: Schematic representation of mitochondrial dysfunction resulting from ovarian energy collapse, culminating in the activation of the intrinsic apoptosis pathway, mediated by the release of cytochrome c and apoptosome formation. Adapted from Barbalho et al. (2024).

inflammation acts as an underlying risk factor for clinical infertility.

From a molecular and risk analysis perspective, Nwhator et al. (2014) quantified the impact of this inflammation on the probability of reproductive success. By correlating the Community Periodontal Index (CPI) with the expression of Matrix Metalloproteinase-8 (MMP-8), the authors observed that an increase in gingival inflammation reduces the chances of pregnancy by 52% (OR: 0.482; P=0.02). In cases of advanced periodontitis, the prognosis becomes even more reserved, with an 84% reduction in the probability of conception (OR: 0.157; P<0.01). It is important to note that although the logistic regression model confirmed the impact of age—with a 15% decline in fertility for each year (OR: 0.842; P<0.01)—the periodontal variable remained a significant independent predictor.

This inflammatory profile and tissue degradation state, evidenced by high MMP-8 activity, are frequently stimulated by specific microbiological activities. Paju et al. (2017) pointed out that the prevalence of the bacterium *Porphyromonas gingivalis* (*Pg*) in saliva is significantly higher in women who did not succeed in conceiving (8.3% vs. 2.1%; P=0.032). Beyond bacterial presence, the host's immune response proves decisive, as the detection of high salivary antibody titers (IgA and IgG) against *Pg* increases the risk of reproductive failure over one year by 3.75 times.

Kamei-Nagata et al. (2025) established that *Pg* acts as a direct disruptor of uterine physiology through its hematogenous dissemination. The pathogen and its lipopolysaccharides (LPS) induce an abnormal and persistent upregulation of estrogen receptor alpha (ER-α) and progesterone receptors (PR) in the endometrium. This molecular disorder prevents the hormonal "silencing" necessary for decidualization, keeping the uterus in a constant proliferative state that renders the implantation window unfeasible. Consequently, the saturation of these receptors nullifies the functional competence of the endometrium, resulting in successive nidation failures and consolidating periodontitis as a critical biological risk factor for female infertility (Kamei-Nagata et al., 2025).

Corroborating these findings, Machado et al. (2020) demonstrated that women referred to fertility clinics presented significantly greater periodontal impairment than the general population. Paradoxically, despite the worse objective clinical condition, these women reported higher levels of oral health-related quality of life compared to the control group. This dissociation between clinical parameters and self-perception suggests a possible cognitive bias or prioritization of goals, in which concern for fertility may reduce subjective sensitivity to periodontal inflammatory signs. This phenomenon reinforces the hypothesis of functional underdiagnosis of periodontitis in this group, supporting the need for systematic periodontal screening in reproductive evaluation contexts.

This scenario of low clinical perception is echoed in global epidemiological data. The World Health Organization (WHO) estimates that severe forms of periodontal disease affect approximately 19% of the global adult population, exceeding one billion cases worldwide. However, patient recognition of the pathology is disproportionate to its prevalence: according to Wiernik et al. (2024), only 19% of individuals

at risk of severe periodontitis are aware of their condition. From a critical standpoint, this perception gap suggests that the psychological urgency for motherhood may intensify a "blind spot" regarding the oral inflammatory state, where the prioritization of immediate reproductive goals relegates asymptomatic oral conditions to the background (Machado et al., 2020).

Thus, periodontitis should be understood as a potentially underestimated systemic factor in the context of female infertility. While therapeutic approaches focus predominantly on hormonal modulation and uterine structural assessment, the persistence of a chronic inflammatory state of periodontal origin may act as a relevant intervening variable. The systemic inflammatory load resulting from untreated periodontium tends to increase the production of pro-inflammatory cytokines and immunological mediators capable of altering endometrial homeostasis. Considering that uterine receptivity depends on a finely regulated immunological balance an indispensable condition for the opening of the implantation window and for adequate decidualization, any systemic inflammatory dysregulation can compromise nidation and reduce the probability of reproductive success (Dekel et al., 2010).

The Periodontium–Ovary–Endometrium Interface in Female Subfertility

Polycystic Ovary Syndrome (PCOS)

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder of complex etiology, centered on the imbalance of the hypothalamic-pituitary-gonadal axis. The pathognomonic feature of this condition is the resistance of the Gonadotropin-Releasing Hormone (GnRH) pulse generator to the negative feedback exerted by progesterone. Consequently, there is a disproportionate secretion of Luteinizing Hormone (LH) relative to Follicle-Stimulating Hormone (FSH), which overstimulates thecal steroidogenesis and results in hyperandrogenemia, interrupting follicular maturation and culminating in chronic anovulation and infertility (Karoline et al., 2025).

Beyond hormonal changes, PCOS is inseparable from a low-grade systemic inflammatory state and metabolic dysfunctions, such as insulin resistance. This immunometabolic profile establishes a two-way street with Periodontal Disease (PD), as both pathologies share identical pro-inflammatory mediators. Women with PCOS frequently present elevated levels of C-Reactive Protein (CRP), Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-6 (IL-6), creating a systemic environment that heightens the inflammatory response in gingival tissues (Machado et al., 2020).

Literature suggests that the severity of periodontal destruction in PCOS patients is mediated by a pathological triad: subclinical inflammation, oxidative stress, and glycemic instability in the gingival crevicular fluid (Dursun et al., 2011). In this scenario, it is noteworthy that besides PCOS, comorbidities such as Metabolic Syndrome and Diabetes Mellitus act as catalysts, intensifying bone attachment loss and tissue degradation (Preshaw et al., 2012; Nibali et al., 2013).

This synergistic interaction promotes a feedback loop: while PCOS inflammation weakens the oral immune barrier, periodontal bacteremia and the translocation of bacterial byproducts into circulation sustain

the pathogenesis of PCOS (Akcali et al., 2017). Reinforcing this molecular connection, Varghese et al. (2019) demonstrated that periodontal comorbidity functions as a potent inflammatory amplifier, doubling the salivary concentration of IL-6 in women with PCOS. Such findings suggest that oral biofilm control may be an important adjuvant strategy to mitigate insulin resistance and ovulatory dysfunctions.

Endometriosis

Currently, science proposes the existence of a periodontium-uterine axis, where endometriosis and periodontitis share an inflammatory identity based on the disruption of immunological homeostasis. Classic epidemiological data have already shown that an endometriosis diagnosis increases the probability of periodontal pathologies by 57% (Kavoussi et al., 2009). However, recent evidence suggests that this relationship transcends mere coexistence: the severity of oral tissue destruction is significantly more pronounced in women with active endometrial foci, indicating a systemic catabolic synergy (Thomas et al., 2018; Machado et al., 2020).

The chronic nature of both diseases serves as the biological pillar of this interaction. In endometriosis, the pelvic microenvironment becomes a production center for cytokines (IL-1β, IL-6, IL-8, and TNF-α) that, via circulation, induce hypersensitivity in the periodontium. Conversely, periodontitis acts as a catalyst for endometrial progression. Through hematogenous dissemination, pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can translocate to the peritoneum (Katz et al., 2009; Song et al., 2024). Once in the pelvic cavity, these microorganisms trigger immune reactions that favor the attachment of endometrial tissue to ectopic sites.

Oxidative stress and molecular signaling consolidate this definitive link. While ROS-rich peritoneal fluid promotes genomic damage and lesion angiogenesis, the periodontal response generates an excess of free radicals that activate transcription factors such as NF-κB and AP-1 (Arunachalam et al., 2015; Thomas et al., 2018). This activation regulates pro-inflammatory genes and matrix metalloproteinases, responsible for both alveolar bone resorption and uterine environment instability. In this sense, periodontitis acts as an aggressive systemic modulator, capable of elevating the inflammatory profile necessary for the maintenance and progression of endometriosis (Song et al., 2024).

The consequence of this inflammatory imbalance is the instability of the uterine microenvironment, with impairment to decidualization, endometrial receptivity, and embryonic implantation. In this scenario, periodontitis configures itself as a systemic modulator of the inflammatory response, potentiating molecular pathways that favor the maintenance and progression of endometriosis and, consequently, compromise female reproductive competence (Song et al., 2024).

Final Considerations

The present study demonstrated that periodontitis acts as a systemic modulator with direct repercussions on female reproductive physiology. The interaction between the periodontium and reproductive organs, particularly the ovary and endometrium, is sustained by an inflammatory-oxidative axis characterized by the persistent release

of pro-inflammatory cytokines and reactive oxygen species. This favors mitochondrial dysfunction in ovarian tissue, impacting cellular bioenergetics and oocyte quality, while simultaneously compromising the endometrial immunological homeostasis required for adequate uterine receptivity. These mechanisms contribute to embryonic implantation failures, providing evidence that links periodontitis to female subfertility.

Clinically, these findings highlight that oral health should not be neglected in assisted reproduction protocols or family planning. The identification of oral pathogens in uterine tissues reinforces the need for interdisciplinary action between dental surgeons and reproductive health professionals. Periodontal management before and during pregnancy presents itself as a primary prevention strategy to optimize time to conception and reduce inflammatory states that exacerbate pathologies such as PCOS and endometriosis.

Although available studies have elucidated relevant mechanisms relating periodontal inflammation to reproductive dysfunction, a significant gap remains regarding the temporality and sequence of these molecular changes. In this sense, the use of animal models remains vital for controlling variables and testing therapies aimed at recovering reproductive functionality under inflammatory stress.

Therefore, the preservation of periodontal health is an inseparable pillar of global reproductive health. The integration of dental care into family planning has the potential to reduce the biological and social burden of infertility, ensuring a favorable biological environment for successful conception. In view of the above, maintaining periodontal integrity can contribute to modulating the systemic inflammatory load and preserving the immunological and endocrine balance necessary for health and reproductive competence.

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