SJIF Impact Factor (2026): 8.863| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 11 | Issue: 5 | May 2026 - Peer Reviewed Journal

IMPACT OF PERIODONTITIS ON FERTILITY OUTCOMES IN PCOS WOMEN

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ABSTRACT

Introduction
Polycystic Ovarian Syndrome (PCOS) is one of the most common endocrine disorders. It commonly affects 7-20% of women of reproductive age. PCOS is interconnected to systemic disorders such as Diabetes mellitus, cardiovascular disorder and psychological conditions. Studies have reported that PCOS has a bidirectional link with periodontitis. According to the recent data, the women with PCOS may more likely suffer from periodontal diseases. They tend to have a compromised periodontal health. Chronic low-grade inflammation is the connecting pathway that links periodontal diseases and systemic disorders.

KEYWORDS: *Polycystic Ovary Syndrome (PCOS), Periodontal disease, Anovulation, Periodontitis, Fertility outcomes.*

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a problem with the hormones that occurs during the reproductive years. It was previously known as "Stein-Leventhal syndrome" or "Polycystic Ovarian disease". By definition, "PCOS is a heterogeneous disorder that is a combination of signs and symptoms of androgen excess and ovarian dysfunction, provided that other specific diagnoses, such as hyperprolactinaemia and nonclassic congenital adrenal hyperplasia, has been excluded [1]. It is a common, complex disease affecting women worldwide [2]. In other countries, the prevalence of PCOS in adult females is 2.2-26% [3]. In India, the prevalence of adolescent girls having PCOS is 9.13-36% [4].

In PCOS, the production of estrogen and androgen are imbalanced which is caused by decreased aromatase activity and increased levels of gonadotropin-releasing hormone [5]. This increased level of gonadotropin-releasing hormone is interlinked with hyperandrogenism which causes increase in ovarian volume resulting in alteration of reproductive cycle in females with PCOS [6]. Chronic anovulation leads to increase sex hormone.

Periodontitis is a complex, multifactorial and inflammatory disease of the supporting structures of the teeth [7]. Globally, Periodontitis is the second most prevalent oral disease [8]. Periodontitis is influenced by genetic, systemic and environmental factors [9]. There is a bidirectional relationship between periodontitis and Polycystic ovarian syndrome [10]. Menstrual irregularities, chronic anovulation and hyperandrogenism are main characteristics feature of PCOS [11]. Periodontitis is a risk factor for many systemic diseases such as diabetes mellitus, dyslipidemia, obesity, cardiovascular diseases (CVDs), rheumatoid arthritis and respiratory diseases [12]. Chronic low-grade inflammation is the reasonable etiologic pathway connecting periodontal disease and systemic disorders [13]. Many studies reveal, women with PCOS are more prone to develop periodontitis [14]. Women with PCOS and untreated periodontitis may result in decreased frequency of decreased ovulation, natural conception rates, decreased IVF success and increase in pregnancy complications.

Two-way link between Periodontitis and PCOS:
Polycystic Ovary Syndrome (PCOS) is the most common heterogeneous disorder in women [15]. It is characterized by hyperandrogenism (HA), Oligomenorrhea or ameorrhea, Polycystic ovary and low-grade inflammation [16]. Hyperandrogenism is a medical condition defined by excess male sex hormones (mainly testosterone) in women, affecting roughly 5% of females of reproductive age. The leading cause is Polycystic Ovarian Syndrome. Oligomenorrhea is a menstrual condition characterized by infrequent periods, typically occurring at intervals greater than 35days, or fewer than 4-9 cycles per year. The main potential complication is infertility or difficulty conceiving due to irregular ovulation. Low-grade inflammation in PCOS is a chronic, low-level immune response where white blood cells produce inflammatory substances. It acts as a bridge between PCOS and long-term risks like heart disease, diabetes and obesity by promoting androgens which disrupt ovulation.

PCOS and periodontal diseases have common risk factors such as metabolic syndrome [17], obesity, diabetes mellitus and cardiovascular disease [18. Several studies have reported the link between PCOS and periodontal diseases [19].

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A recent cross-sectional study shows that women who are infertile, in comparison with those who are fertile are more prone to periodontal diseases. They show signs such as increase in probing depth and clinical attachment loss. Periodontitis is associated with PCOS which is an important cause of infertility [20]. Women with PCOS tend to exhibit poor periodontal conditions such as bleeding on probing, deep probing depth and high plaque index. Controlling PCOS with oral contraceptives and metformin alleviate periodontal inflammation. The risk of periodontitis is increased by 46% in women with periodontal diseases. The initiation and progression of periodontal diseases rely on the interactions between host and oral microecology. Endocrine disorder remodify the microbiota composition in females at reproductive age.

There is a high risk of osteoporosis in women with PCOS [21]. PCOS destructs the bone metabolism of the alveolar bone around the periodontal tissue which inflate the levels of probing depth and clinical attachment loss resulting in alveolar bone resorption [22]. Luteinizing hormone/Follicle stimulating hormone increased in PCOS and decreases the aromatase activity converting androgens into estrogen resulting in hyperandrogenism. Excessive androgen has severe effect on bone anabolism in women. Many reports suggest that hormonal imbalance in PCOS increase resorption of bone and leads to periodontitis.

Immune-endocrine interactions play an important role between PCOS and periodontitis. Low-grade chronic inflammation characterized by PCOS is considered a main influencer to develop periodontitis. The imbalance of oxidation/antioxidant capacity contributes to oxidative damage called oxidative stress (OS). The PCOS-induced OS have a greater impact on gingival inflammation which is linked to periodontitis.

Factors that connect PCOS and Periodontal diseases:

1. Oral Microflora

Periodontitis is a biofilm-induced disease that starts and progresses as a result of interaction between host and microflora. Fusobacterium nucleatum (Fn), an anaerobic bacteria present in supra and subgingival biofilms along with Porphyromonas gingivalis (Pg), Streptococcus gordoni (Sg) and Treponema denticola (Td) increases the formation of biofilm. There is a rise in salivary levels of Pg and Fn in patients who have PCOS when compared to healthy individuals. The number of Pg have the increased correlation with periodontal disease. Periodontitis may increase the risk of PCOS by altering the host metabolism (23).

2. Inflammation

Low-grade chronic inflammation is the hallmark characteristic feature of PCOS. Many studies have reported that the inflammatory cytokines like tumour necrosis factor alpha, C-reactive protein (CRP) and interleukin-6 play a vital role between PCOS and periodontitis. C-reactive protein (CRP) is increased in PCOS. In severe periodontitis, high serum CRP levels and other proinflammatory circumstances may enhance systemic inflammation and oxidative stress leading to Insulin resistance. Periodontitis may increase the White blood cell count (24).

3. Obesity

30-70% of women suffering from PCOS are affected by obesity. PCOS women who have more abdominal fat which causes hyperinsulinemia and result in Insulin Resistance. Inflammation is regulated by cytokines and inflammatory mediators which are released by adipose tissues. Increased levels of CRP, interleukin-6 are linked to PCOS and leads to chronic low-grade inflammation resulting in periodontal disease (25).

4. Oxidative Stress OS

PCOS triggers oxidative stress (OS). A study found that women with periodontitis and PCOS had elevated levels of OS. Compared to women with PCOS, women with periodontal disease show lower total antioxidant levels (26).

5. Bone resorption

Women with PCOS are more likely prone to develop osteoporosis. Hyperandrogenemia, Obesity and Insulin Resistance are considered to contribute to an elevated level of low Bone Mineral Density (BMD) in women having PCOS. In these women, Insulin Resistance decreases the osteoprotegerin (OPG) expression and increases the expression of RANKL, both of which are important for the resorption of bone. Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) is a protein (cytokine) that acts as a key factor in bone metabolism by promoting the formation, activation and survival of osteoclasts. Hormonal imbalance in PCOS-affected women may increase bone resorption and result in periodontitis (27)

6. Hormonal Imbalance

The association seen between PCOS and periodontal diseases coincides with the hypothesis that female sex hormones lead to gingivitis. Women with PCOS may experience estrogen deficiency which decreases bone mineral density. Estrogen insufficiency increases osteoporosis and affects hard and soft tissues of the oral cavity resulting in damage of periodontal tissues leading to periodontitis. Estrogen deficiency results in lower calcium absorption which leads to systemic bone loss eventually progressing to cause periodontitis (28).

Effect of periodontitis on fertility outcomes in PCOS women

Periodontal disease (PD) has been reported to display an increase in the risk of preterm birth, preeclampsia and low birth weight [23]. During the last decades, Observational studies suggest a possible link between chronic periodontitis and adverse fertility outcomes [24]. A recent review promotes the fact that periodontitis is associated with fertility issues such as Polycystic Ovarian Syndrome, endometriosis and bacterial vaginosis [25]. Periodontal diseases may also affect the early phases of pregnancy including

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conception. Approximately 8-15% of the couples suffer from infertility worldwide [26]. A mutual correlation has been seen between periodontitis and both fertility outcomes and infertility [27].

In each typical menstrual cycle, ovulation should occur 14 days before bleeding. If menstrual cycle takes 21 days or more than 35 days with irregular pattern, anovulation should be taken into account [28]. Polycystic Ovary Syndrome, obesity, thyroid disease and idiopathic causes can be the reason for anovulation [29]. Periodontitis leads to systemic inflammation in the human body. Chronic inflammatory conditions acquired by women with poor oral hygiene and poor fertility outcomes. Periodontitis causes decrease in pro-inflammatory cytokines. In periodontitis, cytokines from interleukin-1 family are produced which can cause reduction in the release of hormones that are essential for ovulation. As a result of these mechanisms, ovulation is prevented and embryos are not implanted [30]. Periodontal infection leads to the production of endotoxins and bacterial products in blood circulation resulting in bacteremia in the uterus. It can suppress the efforts to conceive and prevent pregnancy [31]. Regarding female fertilization, it is shown that conception took two months to occur in women with periodontitis. Women trying to conceive naturally or via IVF may experience difficulty in implantation due to cytokine release caused by periodontitis [32].

DISCUSSION

Periodontitis is a complex, multifactorial and inflammatory disease of the supporting structures of the teeth [33]. By definition, "PCOS is a heterogeneous disorder that is a combination of signs and symptoms of androgen excess and ovarian dysfunction, provided that other specific diagnoses such as hyperlactinaemia and non-classic congenital adrenal hyperplasia have been excluded" [34]. In PCOS, the production of both androgen and estrogen are not balanced. It is caused by a decrease in the activity of aromatase and the levels of gonadotropin-releasing hormones are elevated. The elevated levels of gonadotropin-releasing hormones are connected with hyperandrogenism which leads to the increase in ovarian volume thus resulting in the alteration of reproductive cycle in females with PCOS. Chronic low-grade inflammation is main etiologic pathway that connects both periodontal disease and systemic disorders [35].

PCOS is characterized by hyperandrogenism, oligomenorrhea or amenorrhea, Polycystic ovary and low-grade inflammation. Metabolic syndrome, diabetes mellitus and cardiovascular disease are the common risk factors of PCOS and periodontal disease. Bleeding on probing, deep probing depth and high plaque index are the periodontal conditions exhibited by the women with PCOS. Luteinizing hormone/follicle stimulating hormone is elevated in PCOS which decreases the activity of aromatase converting estrogen into androgen resulting in hyperandrogenism. High androgen levels can disrupt ovulation leading to infertility or difficulty conceiving and also has severe effect on bone anabolism in women. PCOS disrupts the bone metabolism of the alveolar bone which increases probing depth and clinical attachment loss and result in periodontitis. The important characteristic feature of PCOS are menstrual irregularities, chronic anovulation and hyperandrogenism. 28% of women with PCOS have a greater risk of acquiring periodontitis.

The early phases of pregnancy including conception may also be affected by periodontal diseases. Periodontitis has been reported to show an increase in the risk of preterm birth, preeclampsia and low birth weight. Periodontitis causes decrease in pro-inflammatory cytokines. These cytokines from interleukin-1 family are produced which can cause reduction in the hormone release that are essential for ovulation. As a result, ovulation is prevented and fertility outcomes becomes compromised. A mutual correlation has been seen between periodontitis and both fertility outcomes and infertility [36]. Within the limited data there seems to be a positive relationship between PCOS and periodontitis.

CONCLUSION

The increased androgen levels, androgen levels, systemic inflammation and microbiological dysbiosis create the pathophysiological basis for the association between PCOS and periodontitis. This results in a greater impact on fertility outcomes. Periodontal assessment should be taken into account for females with PCOS to avoid oral and systemic complication. Gynecologists, endocrinologists and periodontists should collaborate to provide essential care for evaluating systemic and oral health. Regular dental screening should be done to women with PCOS to prevent the risk of developing periodontal diseases. Future investigations are necessary to conclude the association between PCOS and periodontal diseases and another way affect fertility outcome.

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