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Review

ONE OUT OF TEN: WHEN ORAL MEDICINE SHOULD NOT LEAVE BEHIND WOMEN AFFECTED BY REPRODUCTIVE DISORDERS

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ABSTRACT

Female reproductive disorders represent conditions that can significantly impact the overall well-being of women. Research suggests that hormonal changes during menstrual cycles, pregnancy, and menopause can influence the oral environment and contribute to an increased susceptibility to oral diseases, such as periodontitis. Furthermore, polycystic ovary syndrome (PCOS), a common endocrine disorder in women of reproductive age, has been associated with an increased risk of periodontal disease. The underlying hormonal imbalances and inflammatory processes in PCOS may contribute to the higher prevalence and severity of periodontal disease observed in these individuals. Conversely, periodontal disease may have implications for female reproductive health. Evidence suggests a potential link between periodontal pathogens and adverse pregnancy outcomes, including preterm birth, low birth weight, and preeclampsia. The dissemination of oral bacteria and their byproducts into the systemic circulation can trigger an inflammatory response and disrupt the delicate balance essential for a successful pregnancy. This review explores the interrelationship between female reproductive disorders and oral medicine implications, highlighting their potential bidirectional interactions and shared underlying mechanisms. Implementing multidisciplinary approaches combining gynecological and dental care can enhance patient outcomes and improve women's health. Early identification, timely interventions, and preventive measures focused on maintaining oral health through adequate oral hygiene, professional cleanings, and regular dental check-ups are paramount.

KEYWORDS: *PCOS, endometriosis, assisted reproductive technology, periodontitis*

INTRODUCTION

Over the last decades, the scientific community has focused on factors influencing women's health. In particular, the World Health Organization's commitment to "leaving no one behind" is fundamental to achieving the Sustainable Development Goals (SDGs) 3 ("to ensure healthy lives and promote well-being for all at all ages") and SDG 5 ("to achieve gender equality and empower all women and girls") (1-3).

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Women's reproductive health has recently received considerable research and attention. Reproductive health care is crucial to women's well-being, considering the effects of reproductive physiology on the whole body system (4). Reproductive disorders women encounter during their lifetime, which include hormonal therapy as a solution, are polycystic ovarian syndrome, endometriosis, fibroids, and fertility treatments (5).

Hormones are a class of biomolecules that can be taken or secreted into the bloodstream and whose action is reflected in several areas. Oral health has historically been found to be affected by hormonal effects in women. However, through the years, "gender dentistry" has not seen a proper place in scientific research and clinical application.

The aim of this review, in the attempt to fulfill the WHO commitment to "leaving no one behind", is to examine polycystic ovarian syndrome, endometriosis, and fertility treatments and their relationship to oral health.

Polycystic Ovarian Syndrome (PCOS) and periodontal disease: what happens when the endocrine-metabolism is altered?

PCOS is an endocrine disorder affecting the reproductive female system and the metabolic asset in the organism (6). PCOS clinical presentation can be classified into phenotypes. The presentation of PCOS can be categorized into separate phenotypes:

a) when hyperandrogenism (HA), ovulatory disorder (OD), and polycystic ovarian morphology (PCOM) exist;
b) when HA and OD occur;
c) HA and PCOM co-exist;
d) OD + PCOM occur (7).

Due to the alteration of the metabolic and, therefore, endocrine assets, patients affected by PCOS can present symptoms affecting the reproductive system, such as menstrual dysfunction, endometrial dysplasia, and infertility, as well as insulin resistance, diabetes, cardiovascular disease, and obesity (8). In addition, the endocrine and metabolic disorder induces low-grade systemic inflammation by raising pro-inflammatory cytokines.

These alterations are reflected in saliva and oral microbial composition. Indeed, it has been found that oral microbiota is altered in PCOS patients in response to estradiol levels and cases of insulin resistance and obesity, showing how metabolic disease alters microbial metabolomics (6-8). Clinically, this is reflected in a higher susceptibility of PCOS patients to periodontal diseases. Indeed, the alteration of the endocrine and metabolism of the host is reflected in an alteration of the microbial biofilm (8). In addition, the HA, low estradiol level, and insulin resistance alter both bone metabolism and its resistance to injuries and the susceptibility of gingival epithelial cells to infections (8). The increased level of pro-inflammatory cytokines is reflected in periodontal disease inflammation, which can lead to a worsening of the disease (8).

Endometriosis: a systemic disease with relevant aspects in oral medicine

Endometriosis is an inflammatory disease characterized by endometrial-like tissue outside the uterus (9). Being an endometrial-like tissue, it is estrogen-dependent.

Endometriosis aetio-pathology remains unclear. In 2020, García-Peñarrubia et al. proposed a new model of endometriosis development that includes and correlates prenatal exposure to endocrine disruptors, the anogenital distance, and the dysbiosis in the genital tracts (10). This theory is compatible with those previously proposed and placed at the center of endocrine and microbial alteration (10).

Endometriosis lesions may be located in the pelvis, related organs, and distant organs such as the lungs (11). The pelvic pain symptoms and the menstrual stigma still led to a late diagnosis in women and many undiagnosed cases. Due to the endometriosis nature, and the variety of symptoms, which include bloating or nausea, chronic fatigue, and psychological disorders, it should be considered a systemic disease. If we look at oral medicine, endometriosis has been linked to periodontitis, Temporomandibular Joint Disease (TMD), and occasionally endometrial lesions in the jawbone.

In the case of PCOS, the keyword is inflammation in the linkage between endometriosis and periodontal diseases. Endometrial lesions increase the level of oxidative stress and produce chronic inflammation. The pro-inflammatory cytokine in saliva serum can influence the microbial biofilm community and the immune response to periodontal pathogens (12).

Endometriosis is an estrogen-dependent pathology, and we must recall that the temporomandibular joint cartilage presents estrogen receptors responsible for its normal trophism (13). In 2023, Wójcik et al. achieved a preliminary correlation between pelvic pain symptoms in endometriosis patients and TMJ pain (14). The TMJ pain in these patients must be considered with attention. Indeed, in 2022, Brotskyi et al. reported a patient who complained of pain in the temporomandibular area. The clinical and diagnostic investigations revealed the presence of an endometrial lesion in the

temporal bone endometriosis with a consequent TMJ dysfunction (15). Similarly, in 2021, Gala et al. reported an extrapelvic endometriosis lesion in the mandible, initially diagnosed as facial fibroma (16).

Fertility treatment effects on the mineral bone density

The prescription and administration of hormonal therapy in women is becoming frequent to face the systematic effects of menopause and infertility treatments (17). Indeed, fertility in women progressively declines with age until women are no longer able to produce oocytes capable of fertilization well before menopause (17). Menopause is a period strongly associated with bone resorption markers in older women. This phenomenon is probably due to estrogen hormone deficiency and higher follicle-stimulating hormone (FSH) levels in the blood circulation, which increase the risk of osteoporosis up to three times (18). During the menopausal period, an increase in FSH levels and a decrease in estradiol levels will occur, so estradiol does not bind to its receptor in osteoblasts to directly modulate osteoblastic activity and indirectly regulate osteoclast formation (19). As a result, when the estrogen levels decrease, nothing can inhibit the bone resorption process (20). Decreased estrogen will decrease cortical bone matrix production, increase trabecular bone formation, and stimulate bone resorption (20).

Hormonal stimulation is an essential part of modern assisted reproductive technology (ART) (21). Gonadotropin therapy is pivotal in ovarian stimulation. As well acknowledged, whereas FSH is the primary regulator of antral follicular growth, LH enhances steroidogenesis and the development of the leading follicle (21). According to the two-cell two-gonadotropin theory, LH induces androgen production in theca cells, while FSH acts on the proliferation of granulosa cells (GCs) and E_2 synthesis (22). In this context, the main goal of gonadotropin stimulation is to restore adequate E_2 levels. Balanced estradiol levels may determine an improvement in the number and yield of mature oocytes, providing a more physiological pregnancy outcome (23).

There are different applications of gonadotrophic hormones in assisted reproductive technology, and technological advances have led to the production of recombinant forms of human FSH (r-hFSH) and LH (r-hLH) as possible alternatives to the current protocol of therapy (24). Data demonstrated that this gonadotropin stimulation may affect reproductive and bone tissues differently. On the one hand, r-hFSH, used to support ovarian follicle growth in ART, accelerates endometrium maturation, while r-hLH forms improve the follicular environment and insulin sensitivity (25). On the other hand, the use of gonadotropins in ART practice can affect bone health, including the one of the jawbone. As reported by Zhu et al., FSH increases the alveolar bone resorption, activating the cyclooxygenase-2 pathway (26). In addition, FSH up-regulates genes typical of osteoclasts (RANK, MMP-9, and Trap), promoting osteoclast production and alveolar bone resorption. Quantifying the expression of these factors in healthy controls and in patients undergoing ART could provide a more complete view of the effects these treatments can have on patients' oral health years later.

Despite the fact that the hormonal effect of ART has not yet been clinically studied on the alveolar bone changes, few studies evaluate the effect of these hormones on the periodontal state of women who have undergone ART (27, 28). In both studies, gingival and periodontal health worsened after the IVF treatment.

CONCLUSIONS

In conclusion, the interplay between female reproductive disorders and periodontal disease is a complex phenomenon. Understanding the bidirectional relationship between these conditions is vital for healthcare professionals, enabling them to provide comprehensive care that addresses both oral and reproductive health concerns in women. Further research is warranted to elucidate the underlying mechanisms and develop targeted interventions to optimize the health outcomes of affected individuals.

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