REVIEW ARTICLE

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Correlation of Periodontitis and In Vitro Fertilization Outcome: A Literature Review

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Abstract

Background and Aim: This study reviewed the literature regarding the correlation of periodontal disease and outcome of in vitro fertilization (IVF).

Materials and Methods: "IVF", "In Vitro Fertilization", and "Periodontitis" were searched in PubMed, Web of Science, and Google Scholar databases to find English articles published up to August 2022. A free online resource developed by the Canadian Agency for Drugs and Technologies in Health was used to search the grey literature. Duplicate screening and extraction of citations were also carried out. No search filter was applied during searching. Two independent reviewers evaluated the title and abstract of the retrieved articles. Next, the articles retrieved in the initial search were reviewed independently for relevant information to the research question.

Results: The relationship between periodontitis and IVF has been studied in a limited number of studies. According to most articles, periodontal disease may affect IVF implantation and vice versa in women who want to conceive through this procedure. Low sperm motility and reduction in sperm count were also seen in males with periodontitis. Only one study found no correlation between the presence of periodontal disease and unwanted IVF results.

Conclusion: According to the results, periodontitis can impair the reproductive function since it causes systemic bacteremia. Oral health should be addressed by the primary care providers before the onset of any fertility treatment. There is; however, a need for further investigations into the possible implications of periodontal disease in women seeking fertility care.

Key Words: Mouth Diseases; Periodontal Diseases; Reproductive Techniques; Sperm Injections

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Introduction

Periodontitis is the most common chronic inflammatory disease, and the second most common oral disease in adults. Approximately 20%-50% of the population are affected by periodontal disease, which is characterized by inflammation of the tooth supporting structures including the gingiva, cementum, periodontal ligament, and alveolar bone [1- 4]. Although the prevalence of periodontitis may vary, the prevalence of periodontitis as a manifestation of a systemic disease reportedly ranges from 5%-67% and its necrotizing form has a prevalence of < 1% [5, 6]; while its

moderate to severe form has a prevalence of 11% [7]. In most cases, periodontitis occurs after chronic gingivitis which is characterized by bleeding on probing. Periodontitis occurs when the inflammation leads to attachment loss (loss of periodontal ligament and alveolar bone) [8].

The pathogenesis of periodontitis has been the topic of numerous investigations mainly because of its effect on other parts of the human body. A strong correlation has been reported between periodontal health concerns and several systemic diseases, including cardiovascular diseases, diabetes mellitus, obesity, and Alzheimer's disease [1, 7, 9-11]. Patients with periodontitis are more likely to have hypertension in comparison to those without it [9].

Approximately 8%-15% of the couples suffer from infertility worldwide. It simply means that they have tried to conceive for about one year and failed [2, 12]. In about 85% of the cases, there is a clear reason behind the failure in fertilization. The most common reasons for infertility include ovulatory dysfunction, male infertility, and tubal dysfunction. It is estimated that infertility services are used by almost one in eight women between the ages of 15 and 49 years [13]. Each year, a huge amount of money is spent to combat infertility problems, and this issue puts a burden on the healthcare systems worldwide.

Recently, the effects of periodontitis on fertility, infertility treatments, and outcomes of pregnancy have gained increasing attention. A mutual correlation has been proposed between periodontitis and both pregnancy outcome and infertility [4, 14, 15]. However, studies analyzing the association of infertility treatments including in vitro fertilization (IVF) and periodontitis are scarce. Thus, this study aimed to verify the accuracy of this association by a literature review.

Materials and Methods

Search strategy:

This literature review was conducted to answer the following research question:

Is there a possible relationship between periodontal disease and IVF outcome?

"In Vitro Fertilization", "IVF", and "Periodontitis" as keywords were searched in several electronic databases including PubMed, Web of Science, and Google Scholar to find English language articles published up to August 2022. A free online resource developed by the Canadian Agency for Drugs and Technologies in Health was used to search the grey literature as well. No search filter was applied during searching.

In the first step, a two-author review was conducted for each article's title and abstract. Then, the articles included in the initial search were reviewed independently for relevant information to the research question.

Types of studies:

Thirteen articles were identified by searching the keywords in the databases. After omitting the duplicates, 8 articles remained and were analyzed by two different reviewers independently, which led to inclusion of 6 articles in the present review. Amongst them, 5 articles were observational studies and one was a literature review. The main features of each study are summarized in Table 1.

Results

Amongst the included studies, 2 studies examined males and analyzed their fertility parameters such as sperm motility, number of sperms, and the quality of semen [12, 16]. Both studies found a positive link between low sperm motility and presence of either gingivitis or periodontitis. Klinger et al. [12] evaluated some other infertility-related problems such as familial infertility, smoking, and antibiotic intake during the past year, and found these parameters to be the determining factors related to infertility.

Table 1: Summary and main findings of the reviewed articles

First author's name	Aim/purpose	Gender of participants	Methodology	Main findings and results
Pavlatou et al. [2] (2013)	To examine the effects of pre-existing periodontitis on IVF in women and vice versa	Females	Observational study	Periodontal diseases can deteriorate during the IVF* procedure and poor periodontal condition can lead to poorer IVF outcomes
Klinger et al. [12] (2011)	To evaluate the presence of the relation between either gingivitis or periodontitis and the quality of sperms	Males	Observational study	Possible relation between male infertility, diminished semen quality, and presence of periodontal diseases
Chidambar et al. [16] (2019)	To analyze the correlation between parameters of male fertility and periodontal status in patients during IVF procedure	Males	Observational study	Possible relationship between semen quality decline, male infertility, and periodontal diseases
Smadi [17] (2017)	To investigate the effect of IVF on periodontal condition parameters	Females	Observational study	IVF can affect oral health Status
Khanna et al. [27] (2017)	To examine the relationship between fertility treatment outcomes and oral health status	NA*	review	Possible linking between poor oral health and poor reproductive outcomes
Khalife et al. [18] (2019)	To assess the relationship between pre-existing periodontitis and IVF parameters	Females	Observational study	No association between periodontal diseases and IVF outcomes

*IVF: in vitro fertilization, *NA: not applicable

In 3 studies, the samples included women who underwent IVF [2, 17, 18]. Pavlatou et al. [2] examined the relationship of pre-existing periodontitis and the outcome of IVF, and showed an inverse correlation between both gingivitis and periodontitis and the number of follicles and transferred embryos after IVF. The results of Khalife et al. [18] were in contrast to those of Pavlatou et al [2]. Khalife et al. [18] reported that periodontitis did not affect implantation. They explained such results to be related to the diet of the middle eastern patients, which includes a variety of minerals and vitamins that reduce inflammation [18]. Smadi [17] studied the gingival and periodontal changes during IVF and concluded that IVF can negatively affect the oral health status.

Discussion

Based on the "focal theory", a local in situ infection can affect a remote area in the human body and lead to a chronic disease. The Hippocrates was the first to mention an association between oral infections and systemic diseases. He reported a patient suffering from rheumatism after having a tooth extraction [19].

Different microorganisms are involved in periodontitis. The periodontal pocket biofilm can change according to the nutrients present in the pocket and the oxygen supply. *Aggregatibacter actinomy-cetemcomitans* is the first periodontal pocket colonizer which is resistant to oxygen and hydrogen peroxide. *Prevotella nigrescens*, *Porphyromonas gingivalis*,

Fusobacterium nucleatum, *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola* can affect the pregnancy outcomes. Preterm labor and low birth weight are the most common outcomes of periodontitis in pregnant women. Maternal and paternal periodontitis can affect conception and impair the fertility capability. Some experimental studies reported infertility as a secondary outcome in rodents challenged with periodontitis [4, 7, 19, 20].

Periodontitis and female infertility:

Infertility is known as failure in conception after one year of regular unprotected intercourse (at least 2 times a week). In this situation, both male and female should undergo infertility evaluations. If the age of the female partner is over 35 years, 6 months of unprotected intercourse and disability to conceive would suffice to start the evaluations [20,21]. About 8% to 15% of the couples struggle with infertility in today's world. The most common reasons of infertility include ovulatory dysfunction, tubal problems, and male-related factors [13]. The World Health Organization recognizes ovulatory disorders as the cause of 25% of the infertility cases. In each typical menstrual cycle, ovulation should occur 14 days before bleeding. If the menstrual cycle takes less than 21 days or more than 35 days, in an irregular pattern, anovulation should be considered. Polycystic ovary syndrome, obesity, thyroid disease, and idiopathic causes can be the reasons behind anovulation [22].

Between 11% to 67% of infertility diagnoses are related to tubal infertility, characterized by blocked fallopian tubes or tubal incompetence due to pelvic adhesions [13, 23]. About 26% of all infertilities are caused by the fallopian tube blockage or dysfunction. Acute or chronic inflammation of the fallopian tubes is the main cause of this blockage. There is also the risk of infection of the fallopian tubes, impairing their function and preventing conception, which will cause infertility [22].

Periodontitis is a common inflammatory disease of the oral cavity which can lead to systemic inflammation in the human body. Women with poor oral hygiene are at greater risk for infertility due to chronic inflammatory conditions caused by periodontal disease and active carious lesions. Periodontitis causes a reduction in anti-inflammatory cytokines and an increase in pro-inflammatory cytokines. Cytokines from the interleukin-1 family which are produced in periodontitis can reduce the release of hormones that are necessary for ovulation. As a result of these mechanisms, ovulation is prevented and embryos are not implanted [15].

Periodontitis and male infertility:

Male infertility is the reason behind 50% of the failures in conception [21]. Different factors can contribute to male infertility, including genetic mutations, lifestyle choices, and medical conditions [24]. These factors can influence fertility by affecting the level of hormones, sexual ability, and function of the testicular system. Moreover, fertility is negatively affected by the paternal age due to various reasons such as increased mutations, testicular shrinkage, a rise in the level of follicle-stimulating hormone, and a fall in the level of the testosterone hormone which leads to spermatogenesis dysfunction [24, 25].

Sperm quantity and quality can be affected by several factors such as infection. Infection and bacterial colonization can be linked to the concentration and morphology of the semen [4], and presence of periodontitis can be a reason for that. The first hints of a correlation between oral health status and semen parameters date back to 1993 when Bieniek and Riedel [26] found a link between bacteriospermia which was resistant to treatment and dental

foci. After that, different studies were conducted to investigate the association between the oral health status and infertility [4-8, 12, 16, 27, 28]. Práger [29] showed that males with idiopathic infertility had higher bleeding on probing and calculus in comparison to their fertile counterparts. Also, depth of periodontal pockets and the magnitude of attachment loss have been linked to low sperm motility and low sperm count which can cause fertility problems, especially in patients aged 33 to 38 years [4].

Periodontitis and IVF:

IVF is a treatment option for infertile couples. About 2 million cycles of this procedure are performed annually worldwide. In IVF, various medications are used to stimulate superovulation or control the time of ovulation. This process causes the secretion of a huge amount of estradiol up to 1000-4000 pg/mL. The success rate of IVF depends on a wide range of variables such as the couples' age, family history, medication intake, and presence of unhealthy lifestyle habits such as smoking. Infection or inflammation can also affect the production of oocytes during IVF [17].

Periodontitis is the most common chronic disease affecting adults worldwide. A complex interaction exists between the oral microflora and periodontal environment in humans. It is estimated that over 200 species of bacteria are involved in apical periodontitis, and more than 500 species are involved in marginal periodontitis [27]. Some studies supported the presence of a mutual relationship between the oral health status and IVF outcome [2, 12, 13, 16-18, 27]. Periodontal infection can lead to production of endotoxins and bacterial products in the blood circulation causing bacteremia in the uterus. It can hinder the efforts to conceive, and can also prevent pregnancy [13, 15, 27]. On the other hand, IVF can stimulate inflammation in the gingiva and tooth supporting structures [2].

IVF can deteriorate both gingivitis and periodontitis in females. The level of gingival inflammation increases significantly with no change in dental plaque level in women undergoing IVF [12]. Medications taken during this treatment and changes in sex steroids have different effects on the oral health status. One reason behind the aggravated gingivitis and periodontitis in IVF patients is that high levels of exogenous progesterone can enhance the estrogen's effects on patients as an adjuvant therapy during the luteal phase of IVF, and the progesterone rise can increase vascularity of the gingiva and other oral tissues. In addition, presence of prostaglandins in the gingival crevicular fluid modulates the inflammatory responses through several mechanisms, such as an increase in production of prostaglandins, polymorphonuclear leukocytes, and prostaglandin E2 during IVF [17].

Periodontitis can cause an increase in pro-inflammatory cytokines, which negatively affects male and female fertilization capacity. These cytokines include tumor necrosis factor-alpha, interleukin (IL)-1, and IL-6, in serum and/or gingival crevicular fluid [30]. It was shown that IL-6 levels were significantly higher in the seminal plasma of infertile or immunoinfertile males than fertile controls. Moreover, the immune response to heat shock protein which is possessed by *Porphyromonas gingivalis* can be related to silent male genital tract infections and infertility. High interleukin levels in seminal plasma and leukocytospermia are frequently associated with IgA antibody levels produced against heat shock protein 60 in seminal fluid [31]. Regarding female fertilization, it was shown that conception took two extra months to occur in women

with periodontitis [22]. In addition, women trying to conceive naturally or via IVF may experience difficulty in implantation due to cytokine release caused by periodontitis [27].

Conclusion

There is a possibility of conception being hindered by systemic bacteremia caused by subclinical infections like periodontitis. Low sperm motility and reduction of semen quality in males and prevention of implantation and reduction in the number of mature follicles and embryos are among the effects of periodontitis on the IVF outcome. In addition, IVF can aggravate the oral health status by altering the level of sex hormones and medication intake. Thus, oral health should be addressed by the primary care providers before the onset of any fertility treatment. There is; however, a need for further investigations into the possible implications of periodontal disease in women seeking fertility care.

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Conflict of interests

There is no conflict of interests to declare.

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