

Review Article

Periodontal Health and Fertility: Is there any Relationship?

Varun S¹ and Bharti J^{2*}¹Public Health Dentistry, Rayat Behra Dental College, India²Department of Obstetrics & Gynaecology, Post Graduate Institute of Medical Education and Research, India***Corresponding author:** Joshi Bharti, Department of Obstetrics and Gynecology, Old Nehru Hospital, Post Graduate Institute of Medical Education and Research Chandigarh, India**Received:** October 12, 2016; **Accepted:** November 27, 2016; **Published:** November 29, 2016**Abstract**

Periodontal disease is a chronic microbial infection of gums and surrounding tissues. The host response to bacterial infection results in overproduction of cytokines and other inflammatory markers which has been held responsible for various systemic conditions like diabetes, respiratory disease, adverse pregnancy outcomes and cardiovascular events. In recent years few studies have thrown light on the association of periodontitis with infertility and concluded that there could be possible association between periodontal disease and woman's chance of conception and effectiveness of infertility treatment. The evaluation of periodontal clinical parameters within IVF programme is a new field of research with limited information. Furthermore, effect of bacteriospermia secondary to periodontal disease resulting in decreased sperm motility or count or increased sperm apoptosis remain to be determined as only few studies have mentioned about these effects. Nevertheless, the confirmation of real association of periodontal disease with male and female infertility requires further prospective randomized trials and interventional studies. There is a need of coherent approach between gynaecologists and dentists to verify the existing relation which may establish the background for need of periodontal treatment upon diagnosis before embarking on infertility treatment.

Keywords: Periodontal disease; Infertility; Association; Periodontitis; Fertility

Introduction

Periodontitis is a chronic inflammatory disorder of gums & surrounding tissues caused by specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both. The clinical feature that distinguishes periodontitis from gingivitis is the presence of clinically detectable attachment loss. Gingivitis is milder reversible inflammation of the soft tissues around teeth while periodontitis is severe form of periodontal disease resulting in the destruction of the alveolar bone supporting structures & soft tissues [1]. Oral health is gaining lot of importance in recent times and has been associated with almost all the disease states of the body i.e. Respiratory, cardiovascular diabetes and adverse pregnancy outcomes [2-5]. Infertility affects around 15% of the couples worldwide and can be due to many factors like tubal, ovulatory or male factor. Around 30% of cases of infertility are unexplained. Till date little is known about the effect of periodontal disease on reproductive function and evidence to support a link between periodontitis and subfertility is still emerging. In the last few years focus of researchers has been on the role of periodontitis in infertility. Whether oral health status plays any part in subfertility of the partners, was the question in our mind. With this hypothesis that fertility is compromised in people with chronic dental diseases, we searched the literature and reviewed the studies published till now in this article.

Methodology

Various studies published so far were searched and review was carried out to verify the existing research about the association

between periodontal diseases and female infertility, and the biological rationale for such relation. After a judicious literature investigation, it is possible to state that there is insufficient evidence to confirm the association until now. More studies proposing to investigate that relation are, thus, necessary.

Evidence of effect of periodontal diseases on female fertility

The term infertility is defined as failure of a woman to conceive after one year of unprotected intercourse. Regarding the effect of periodontal disease on the female fertility, it has been interpreted that gram negative bacteraemia resulting from periodontal inoculous incites the immune mechanism and triggers the overproduction of pro-inflammatory markers like tumour necrosis factor alpha (TNF- α), interferon gamma (IFN- γ) and interleukin 1 beta (IL-1 β) etc [6]. This has been strongly supported by various studies identifying that even subclinical infection significantly affects conception rate. Significant failure rate in achieving pregnancy despite the fact that there has been appreciable progress in the knowledge and techniques to treat infertility has recently raised concern regarding the role of periodontal disease in infertility [7-10]. The question arises whether the chronic infection from periodontal disease directly affects endometrium or influences the effectiveness of hormonal therapy used to treat infertility or indirectly associated with other subclinical infections causing infertility [11,12]. The answer to the above seems to be difficult but the possible mechanisms supported by available literature may be due to local endometrial effect or other mechanism which is not clear. Collective evidence so far suggest that successful treatment of periodontal disease have led to improvement

in endothelial and vascular function and reduction in the level of inflammatory markers.

Endometrial effect of periodontitis is corroborated by several studies [13-16]. This has been explained in similar fashion to other inflammatory conditions such as hydrosalpinges, endometritis and polycystic ovarian syndrome in which it is hypothesized that negative influence on conception relates in part to an endometrial effect. A cross-sectional study aimed to explore the relation between time to conceive and periodontitis by Nwhator, et al. [17] concluded that there is significant association between periodontal disease and conception time. He further suggested that women of reproductive age group should have periodic dental checkup and maintain good oral hygiene.

The answer to the fundamental question that periodontal infection not only affect reproductive potential but also alters success and treatment outcome of infertility has barely been explored [18,19].

Effect of periodontal health on infertility treatment

Haytec, et al. [18] compared the women receiving ovulation induction drugs either oral or injectable with control group and made reference regarding the impact of medication (ovulation induction drugs) on gingival tissues. The findings of the study revealed significant increase in gingival inflammation in medication group. There was also statistically significant increase in gingival volume and bleeding tendency on probing and duration of medication was almost three months. Potential mechanism for this is increased level of estrogen and progesterone by the usage of ovulation induction drugs. Therefore effective plaque treatment and constant periodontal monitoring should be considered to minimize the effect of periodontal infection on the success of infertility treatment [20]. Transient elevation of inflammatory markers have been shown after periodontal treatment so, it is advisable to wait for few weeks before seeking fertility intervention [21,22]. Hart reported that magnitude of negative influence of periodontal disease on time to conceiving was of the same order as obesity. A large cohort of women who were taking part in "SMILE study" were followed and analyzed information on conceiving time and pregnancy outcomes [23,24]. This was the first report to suggest that periodontal disease may be one of the modifiable risk factor limiting conception and therefore infertile couples may consider dental health checkup before embarking on infertility treatment.

Endometriosis is an important cause of infertility and possible association between periodontal disease and endometriosis was investigated by cross-sectional survey over a period of 5 years [10]. Author concluded that women with self-reported endometriosis had significantly (57%) higher odds of having both gingivitis and periodontitis relative to not having periodontal disease, compared with women without self-reported endometriosis, when controlling for other relevant factors.

The evaluation of periodontal clinical parameters within IVF programme is a new field of research and this fact was first investigated by Pavlatou [25]. Sixty women undergoing IVF were recruited in the study and various indices i.e., Gingival index, bleeding on probing, plaque levels were recorded for all participants before and after IVF. It was observed that aggravation of gingival inflammation was

found after hormonal administration as IVF programme and poor periodontal status before IVF was associated with more failures. Whether this increased gingival inflammation affects the final fertilization of ova needs further investigation.

Few years later in another investigation by same author regarding possible effect of periodontal status on effectiveness of IVF concluded that maternal dental status not only gets affected by hormonal treatment but also may determine the success of IVF [26,27].

Evidence of effect of periodontal diseases on male fertility

Male factor is responsible for about 40% cases of infertility and endocrine function or testicular abnormalities are the main attributable causes. The first study evaluating possible association of men's infertility with poor oral health involved 36 men with bacteriospermia who were resistant to antibiotic therapy [28]. They were segregated into experimental and control group and after six months semen analysis of experimental group showed significant improvement in all semen parameters. This observation of positive correlation of male factor infertility with periodontal disease is supported by many studies [17,29,30]. High level of bacteriospermia and increased inflammatory markers secondary to periodontitis leading to Oligospermia, inhibiting sperm motility and inducing sperm apoptosis are the proposed aetiologies for male infertility [10]. A study by Klinger, et al. postulated that periodontal pockets lead to decreased sperm motility and increase risk of male infertility.

Pitfalls in literature

Most of the studies in literature mention about difficulty in ruling out all confounders and many are limited by small number of sample size. In a study by Nwhator, et al. [17] effect of stress and evaluation of spouse was not considered, which could be a possible cause of infertility. Author has also acknowledged that prevalence of other fertility related variables like fibroid, PCOS, obesity and tubal disease also may have affected the result. Hart, et al. [15] found positive correlation of periodontal disease with infertility in Non caucasian women only and this only reflects positive correlation with conceiving time not with infertility. This could be because of different immunogenicity in different races. A good number of studies support that people with increased immunogenicity are more susceptible to periodontal diseases [31-33] and on the other hand various immunological mechanisms are held responsible for poor reproductive performance and adverse obstetric outcomes. It is clear from recent reports that modulation of immunogenicity leads to increase chance of conception [34,35]. Most of the studies are observational or cross sectional surveys.

Most of the studies establishing correlation between periodontal disease and male infertility remain unadjusted for smoking, diabetes, alcohol and heart disease [17,29,31,36-38]. In a study by Haytec, et al. [18] although gingival inflammation was significantly increased in experimental group but this did not determine that whether it was in healthy or diseased periodontium. So additional prospective studies taking into account the confounders are required to establish real association between periodontal disease and infertility.

Periodontal diseases are multifactorial and due to many different periodontal diseases definitions the comparison among them is still a challenge [39-45]. Experimental animal model studies may benefit

Table 1: Study Characteristics.

Author/year	Location/study design	Sample Characteristics	Main Variables	Main Results
[17]	Nigeria Case-control	70 pregnant and 58 non-pregnant - Periodontal examination: with various indices	1. Time to conceive. (More than one year) 2. Periodontal parameters	There were greater odds of conception within one year for the subgroup with good oral hygiene.
[43]	Australia Cross-sectional	Total 1956 women -516 With periodontal pockets \geq 4 mm -1439 Without periodontal disease	1. Prevalence of periodontal disease 2. Duration to conceive	Periodontal disease might affect time to conception but only statistically significant in the non-Caucasian
[7]	Australia Editorial	N/A	N/A	Women planning for conception should have good oral health and treatment should start early before embarking on infertility treatment.
[28]	Aachen	36 male with bacteriospermia resistant to antibiotic therapy divided in two groups	Various semen parameters	Significant improvement in all semen parameters
[44]	Brazil Animal Experimental Study	Wistar rats -13 periodontally healthy control group -27 induced ligature periodontitis group	Prematurity Fetal weight ,inflammatory markers, placenta, cord	Ligature-induced periodontitis did not result in adverse pregnancy outcomes Infertility was a secondary outcome found in the periodontitis group
[45]	United States Animal Experimental Study	Murines 8 blank control 8 negative control 12 <i>Campylobacter rectus</i> infection 12 <i>Campylobacter rectus</i> and <i>Porphyromonas gingivalis</i> infection	Fecundity Histologic placental inflammation	Reduced fertility Fetal resorption Placental inflammation with necrosis areas Infertility was a secondary outcome found in the oral infected group

by the ability to control the highest number of variables potentially affecting the outcomes studied (Table 1).

Conclusion

Although literature has several reports concluding the association of periodontal disease with male & female infertility, there are inconsistencies regarding result of these studies. Collective evidence suggests that periodontal infection may increase the risk of infertility because of overproduction of pro-inflammatory markers into the systemic circulation. Despite the lack of convincing evidence to confirm real association between two, periodic dental check-up and management of periodontal disease should be considered in all women of reproductive age group. We believe that all females seeking infertility treatment should undergo proper counselling and screening for periodontal disease. There is a need of coherent approach between gynaecologist and dentist and further interventional prospective randomized studies are required to substantiate the correlation between periodontal infection and infertility.

References

- Burt B. Position paper: epidemiology of periodontal diseases. *J Periodontol.* 2005; 76: 1406-1419.
- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol.* 1996; 67: 1085-1093.
- Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. *Oral Dis.* 2008; 14: 191-203.
- Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol* 1996; 67:1103-1113.
- Scannapieco FA. Role of oral bacteria in respiratory infection. *J Periodontol.* 1999; 70:793-802.
- Graves D. Cytokines that promote periodontal tissue destruction. *J Periodontol.* 2008; 79: 1585-1591.
- Hart R. Periodontal disease: could this be a further factor leading to subfertility and is there a case for a prepregnancy dental check-up? *Womens Health* (Lond Engl). 2012; 8: 229-230.
- Camejo MI, Segnini A, Proverbio F. Interleukin-6 (IL-6) in seminal plasma of infertile men, and lipid peroxidation of their sperm. *Arch Androl.* 2001; 47: 97-101.
- Matalliotakis IM, Cakmak H, Fragouli Y, Kourtis A, Arici A, Huszar G. Increased IL-18 levels in seminal plasma of infertile men with genital tract infections. *Am J Reprod Immunol.* 2006; 55: 428-433.
- Kavoussi SK, West BT, Taylor GW, Lebovic DI. Periodontal disease and endometriosis: Analysis of the National Health and Nutrition Examination Survey. *Fertil Steril.* 2009; 91: 335-342.
- Goepfert AR, Jeffcoat MK, Andrews WW, Faye-Petersen O, Cliver SP, Goldenberg RL, et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. *Obstet Gynecol.* 2004; 104: 777-783.
- Goldenberg RL, Culhane JF. Preterm birth and periodontal disease. *N Engl J Med.* 2006; 355: 1925-1927.
- Weiss G, Goldsmith LT, Taylor RN, Bellet D, Taylor HS. Inflammation in reproductive disorders. *Reprod Sci.* 2009; 16: 216-229.
- Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BW. Surgical treatment for tubal disease in women due to undergo *in vitro* fertilisation. *Cochrane Database Syst Rev.* 2010: CD002125.
- Hart R, Norman R. Polycystic ovarian syndrome -Prognosis and outcomes. *Best Pract Res Clin Obstet Gynaecol.* 2006; 20: 751-778.
- Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on *in vitro* fertilization. *Fertil Steril.* 2002; 77: 1148-1155.
- Nwhator S, Opeodu O, Ayanbadejo P, Umezudike K, Olamijulo J, Alade G, et al. Could periodontitis affect time to conception? *Ann Med Health Sci Res.* 2014; 4: 817-822.
- Haytaç MC, Cetin T, Seydaoglu G. The effects of ovulation induction during infertility treatment on gingival inflammation. *J Periodontol.* 2004; 75: 805-810.
- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine.* 18th ed. NewYork: Mc Graw Hill Companies Inc; 2012.
- Lalasa G, Murthy KV, Pavankumar S, Raju GR. Periodontal status in infertile women attending *in vitro* fertilization clinics. *Indian J Dent Res.* 2014; 25: 50-53.

21. Gibbs RS. The relationship between infections and adverse pregnancy outcomes: an overview. *Ann Periodontol*. 2001; 6: 153-163.
22. Kekschull M, Demmer RT, Papapanou PN. 'Gum bug, leave my heart alone!'--epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. *J Dent Res*. 2010; 89: 879-902.
23. Newnham JP, Newnham IA, Ball CM, Wright M, Pennell C, Jonathan S, et al. Treatment of Periodontal Disease During Pregnancy. *Obstet Gynecol* 2009; 114:1239-1248.
24. Hart R, Dorota A, Doherty DA, Craig E, Pennell CE, Newnham JP, et al. Periodontal disease: a potential modifiable risk factor limiting Conception. *Human Reproduction*. 2012; 27: 1332-1342.
25. Pavlatou A. Gingival alterations of women during *In Vitro* fertilization: clinical study. Master's thesis. University of Athens. 2003.
26. Pavlatou A. Influence of the periodontal condition on the success of *In Vitro* fertilization: Clinical and microbiological data. Doctoral Dissertation. University of Athens. 2013.
27. Pavlatou A, Tsami A, Vlahos N, Mantzavinos T, Vrotsos I. The effect of *In Vitro* fertilization on gingival inflammation according to women's periodontal status: clinical data. *J Int Acad Periodontol*. 2013; 15: 36-42.
28. Bieniek KW, Riedel HH. Bacterial foci in the teeth, oral cavity, and jaw-secondary effects (remote action) of bacterial colonies with respect to bacteriospermia and subfertility in males. *Andrologia*. 1993; 25: 159-162.
29. Klinger A, Hain B, Yaffe H, Schonberger O. Periodontal status of males attending an *in vitro* fertilization clinic. *Journal of Clinical Periodontology*. 2011; 38: 542-546.
30. Zhu C, Qin Z, Huang H, Li X, Feng Y. The correlation study between male infertility and chronic periodontitis. *China Modern Medicine*. 2010.
31. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol*. 1997; 24: 72-77.
32. Galbraith GM, Steed RB, Sanders JJ, Pandey JP. Tumor necrosis factor alpha production by oral leukocytes: influence of tumor necrosis factor genotype. *J Periodontol*. 1998; 69: 428-433.
33. Kornman KS, di Giovine FS. Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis. *Ann Periodontol*. 1998; 3: 327-338.
34. Winger EE, Reed JL, Ashoush S, Ahuja S, El-Toukhy T, Taranissi M. Treatment with adalimumab (Humira) and intravenous immunoglobulin improves pregnancy rates in women undergoing IVF. *Am J Reprod Immunol*. 2009; 61: 113-120.
35. Winger EE, Reed JL, Ashoush S, El-Toukhy T, Ahuja S, Taranissi M. Degree of TNF-alpha/IL-10 cytokine elevation correlates with IVF success rates in women undergoing treatment with Adalimumab (Humira) and IVIG. *Am J Reprod Immunol*. 2011; 65: 610-618.
36. Javed F, Romanos G E. Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: Downloaded from A systematic literature review. *J Periodontol*. 2009; 80: 1719-1730.
37. Kataria G, Saxena A, Bhagat S, Singh B, Kaur M, Kaur G. Deep neck space infections: A study of 76 cases. *Iran J Otorhinolaryngol*. 2015; 27: 293-299.
38. Segura-Egea JJ, Martin-Gonzalez J, Castellanos-Cosano L. Endodontic medicine: Connections between apical periodontitis and systemic diseases. *Int Endod J*. 2015; 48: 933-951.
39. AlJehani YA. Risk factors of periodontal disease: review of the literature. *Int J Dent*. 2014; 182513.
40. Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. *Periodontol* 2000. 1997; 14: 9-11.
41. Borrell LN, Papapanou PN. Analytical epidemiology of periodontitis. *J Clin Periodontol*. 2005; 32: 132-158.
42. Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol*. 2008; 35: 385-397.
43. Hart R, Doherty DA, Pennell CE, Newnham IA, Newnham JP. Periodontal disease: a potential modifiable risk factor limiting conception. *Hum Reprod* . 2012; 27: 1332-1342.
44. Fogacci MF, Barbirato DS, Amaral CS, da Silva PG, Coelho Mde O, Bertozzi G, et al. No Association Between Periodontitis, Preterm Birth or Intrauterine Growth Restriction: Experimental Study in Wistar Rats. *Am J Obstet Gynecol*. 2016; 214: 749.e1-749.e11.
45. Arce RM, Barros SP, Wacker B, Peters B, Moss K, Offenbacher S. Increased TLR4 expression in murine placentas after oral infection with periodontal pathogens. *Placenta*. 2009; 30: 156-162.