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Research Article

Periodontitis and Infertility: An Evidence-Based Review

Abstract

Periodontal diseases are initiated by a pathogenic biofilm, in a susceptible host, affecting the tooth periodontium. Its possible association with many biologic systems has been studied. In this evidence-based review, a comprehensive literature search was carried out to assess if there is an association between periodontal diseases and female infertility. An extensive search was conducted in PubMed and Cochrane Library. Epidemiological studies, experimental studies, inquiries or editorials on the theme periodontitis and infertility published until May 2016 were included. The initial search retrieved 47 papers, from which six were selected due to inclusion criteria. The epidemiological study with the highest level of evidence concluded that periodontal disease might be a factor that increases the time to conception, on average, in two months more, which is as negative as obesity. The authors stated that all patients before attempting to conceive could be oriented to have a dental checkup, as they are currently advised to smoking discontinuation, weight loss, and folate supplementation. The experimental studies pointed out that the infertility problem is a secondary outcome in rodents challenged with periodontitis. The possible biological explanation is that periodontitis causes a systemic inflammation, which could: a) prevent ovulation; b) prevent implantation of the embryo or does not sustain its implantation. It is known that oral health incorporation into general health agenda is crucial for optimal health and general wellbeing. Therefore, women trying to conceive should be in the best possible health, which will be achievable through an effective multidisciplinary teamwork.

(Periodontal Diseases OR Disease, Periodontal OR Diseases, Periodontal OR Periodontal Disease OR Periodontitis OR periodontitis OR chronic periodontitis OR aggressive periodontitis OR periodontal pocket) AND (Fertility OR Infertility OR Sterility OR Reproductive Sterility OR Reproductive Sterility OR Subfertility OR Sub-Fertility OR time to conception OR time to conceive)

Study selection

The inclusion criteria were epidemiological or clinical studies, experimental / animal model studies, inquiries or editorials on the theme periodontitis and infertility, published until May 2016. Letters to the editor, narrative reviews, and articles bringing out other endocrine or reproductive diseases that were not about infertility were not included.

The first selection was conducted after the title and abstract reading, establishing which publications fit inclusion criteria, and could be chosen to take part in the review. References were selected for full-text reading when it was not possible to determine if the inclusion criteria were attended by their title and abstract. Additionally, the reference lists of the publications identified were searched for possible studies that did not come up in the initial search.

After the selection, all papers were read in full and then grouped by study design. Main methods, results and conclusions were described for each article. Also, the strength of the evidence was analyzed, according to the Oxford Centre for Evidence-Based Medicine [12], key findings highlighted and limitations listed.

Results

The initial search retrieved 47 papers, from which 40 were excluded, and one was duplicated. Thus, six publications remained

Introduction

Periodontal diseases are a group of conditions usually initiated by a pathogenic biofilm, in a susceptible host, affecting the periodontium tissues that protect and support the tooth, named as gingivitis or periodontitis, respectively [1]. In the last decades, the concept of inflammatory conditions that act as a reservoir of pathogens and its toxins that may gain the circulatory and the lymphatic systems, causing damage in other places than the mouth are in the spotlight of research in the Periodontics topic, known as Periodontal Medicine [2]. Periodontitis and its possible association with many biologic systems as circulatory, urinary, respiratory, nervous and reproductive have been studied [3-9]. More recently, the relationship between periodontal diseases and women infertility has been investigated [10]. In this evidence-based review, a comprehensive literature research was carried to assess that issue and answer the question: Is there an association between periodontal diseases and female infertility, and what is the biological rationale for such relationship?

Methods

This evidence-based review was conducted to gather results from the majority of the studies published evaluating the subject of periodontitis and infertility issue. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [11], was consulted for reporting this review.

Data sources

An extensive search was conducted in the databases PubMed and Cochrane Central Register of Controlled Trials - Cochrane Library. The strategy search used the following descriptors:

to be fully read (Figure 1). There were two epidemiological studies [10,13], one inquiry [14], one editorial [15] and two experimental studies [16,17]. Studies main characteristics are presented in Table 1.

Epidemiological evidences

Four years ago, a first study hypothesizing that periodontal disease would increase the time to conception was published [10]. Until now this is the highest level of evidence paper published in the subject.

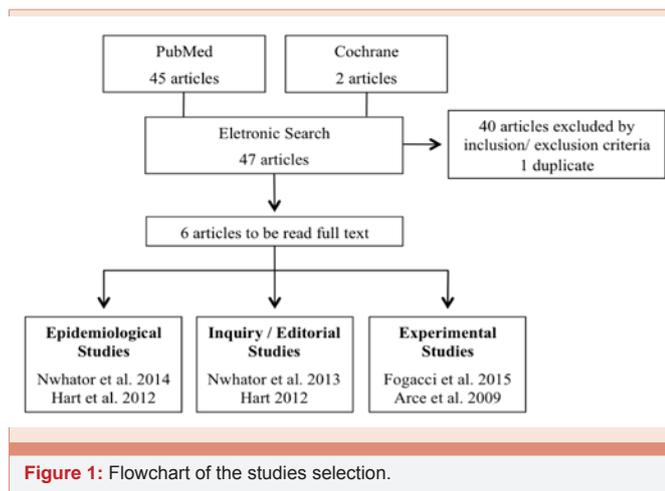


Figure 1: Flowchart of the studies selection.

The authors conducted a randomized controlled trial of treatment for periodontal disease in mid-pregnancy in Australia, in which pregnant women were invited to participate if periodontal disease (defined as the presence of periodontal pockets ≥ 4 mm in depth at 12 or more probing sites in fully erupted teeth) was diagnosed. Women were asked whether planning the pregnancy, the time to conceive and the fertility treatments conducted, if any, and which ones. An observational study was conducted within the major one, on the prevalence of periodontal disease in pregnant women in the second trimester, and the possible association between the oral infection and the time taken to conceive. A sample size of 3416 women was analyzed. From the 2402 women with periodontal disease, 1439 had planned pregnancies and from 1014 without periodontal disease, 517 had planned pregnancies. Those women, whose pregnancy was planned, were stratified by duration until pregnancy (<12 months versus >12 months). The prevalence of periodontal disease was significantly higher in the group in which time to conceive was >12 months. A multivariable logistic regression pointed that non-Caucasian women with periodontal disease had an increased risk of having time to conception >12 months. Authors were careful in conducting the regression including other simultaneously statistically significant risk factors to limited conception (maternal age, body mass index and smoking). An unclear issue is whether severe forms of periodontal disease would enhance the risk to delay pregnancy. A discriminate analysis could have been performed to clarify that. The

Table 1: Studies main characteristics.

Author / Year	Location / Study Design	Sample Characteristics	Main Variables	Main Results
Nwhator et al. 2014 [13]	Nigeria Case-control	70 pregnant and 58 non-pregnant Periodontal examination: oral hygiene index score, the community periodontal index and the periodontitis risk score using matrix metalloproteinase-8	1. Time to conceive (<1 year and >1 year) 2. Periodontal parameters	There were greater odds of conception within one year for the subgroup with good oral hygiene. The study reinforces the need for periodontal examination in women trying to conceive
Hart et al. 2012 [10]	Australia Cross-sectional	1956 Mid-pregnant 516 With periodontal pockets ≥ 4 mm at 12 or more sites in fully erupted teeth 1439 Without periodontal disease	1. Planned pregnancies stratified by duration until pregnancy (<12 months or >12 months). 2. Prevalence of periodontal disease	Periodontal disease might affect fertility, increasing the time to conception in 2 months, on average, but only statistically significant in the non-Caucasian
Nwhator et al. 2013 [14]	Nigeria Inquiry	111 specialists and 8 general practitioners participated in the online survey	Dental history taking, dental/periodontal consultation, and opinion on link between periodontitis and sub-fertility. All self-assessed using close-ended questions	75 professionals were managing sub-fertility patients. 7 elicited dental history, and only 1 requested a periodontal/dental consultation for the sub-fertility patient under care
Hart 2012 [15]	Australia Editorial	N/A	N/A	Women attempting to conceive should be in the best possible health state The intervention should commence early enough to favor implantation and improve pregnancy outcomes
Fogacci et al. 2015 [17]	Brazil Animal Experimental Study	Wistar rats 13 periodontally healthy control group 27 induced ligature periodontitis group	Prematurity Fetal weight IL-1 α , TNF- α , IFN- γ , and IL-12p70, -4, -6, -10, and -17a levels in gingiva, serum, placenta, cord, and amniotic fluid Fecundity	Ligature-induced periodontitis did not result in adverse pregnancy outcomes Infertility was a secondary outcome found in the periodontitis group
Arce et al. 2009 [16]	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	Fetal weight Fecundity Histologic placental inflammation	Reduced fetal weight Reduced fertility Fetal resorption Placental inflammation with necrosis areas Infertility was a secondary outcome found in the oral infected group

(N/A: not applicable, IL: interleukin, TNF: tumor necrosis factor, IFN: interferon).

study conclusion was that periodontal disease might be a factor that affects fertility, increasing the time to conception in two months, on average, which is as negative as obesity, for example, but only statistically significant in the non-Caucasian population. The authors stated that, in the future, all patients before attempting to conceive could be oriented to have a dental check-up, as advised to smoking discontinuation, weight loss, and folate supplementation for example.

Another epidemiological study, with less level of evidence than the previously mentioned, was conducted in Nigeria, with a convenience sample, and cross-sectional, case-control type [13]. The periodontal examination comprised the oral hygiene index score, the community periodontal index (CPI) and the periodontitis risk score using matrix metalloproteinase-8 (MMP-8). A total of 128 women, 70 pregnant and 58 non-pregnant participated in the study. The only CPI score significantly different between the groups was score 2. The non-pregnant group showed significantly more calculus deposits than the pregnant one. Inside the pregnant group, some analyses were still performed. There were greater odds of conception within one year for the subgroup with good oral hygiene (not statistically significant). Also, when grouping all women by age, only the segment 38-42-year-old age group showed significant periodontitis risk for the non-pregnant group, evaluated with the chair-side MMP-8 immunoassay kit. Observations from this study need to be treated with caution due to the limited sample size and study design. Besides, the possible confounders associated with time to conception and infertility were not evaluated. The authors recommend that women in bearing age should be encouraged to have regular preventive dental checkups to maintain good oral health. The study lacks the power to establish a causal association between both conditions but reinforces the need for periodontal examination in women trying to conceive.

An inquiry study was conducted as a questionnaire-based online survey, with Nigerian doctors, about their clinical practice on taking patients dental history, dental/ periodontal consultation, and opinion on the link between periodontitis and sub-fertility [14]. A non-random sampling technique was employed, and the variables were self-assessed by e-mail using close-ended questions. One hundred and eleven specialists and eight general practitioners participated in the online survey. There were 75 professionals managing sub-fertility patients, from which seven elicited dental history, and only one requested a periodontal/dental consultation for the sub-fertility patient under care. Respondents that did not know the type of link between gum disease and sub-fertility were 64.7%. Only 17% of respondents opined that periodontitis could directly predispose to sub-fertility. It was discussed that there are a general apathy and lack of knowledge about dental conditions, particularly periodontal diseases among doctors. The authors believed that the low level of awareness of a possible link between sub-fertility and periodontitis is unacceptable, irrespective of years of basic medical or specialist experience.

In an editorial paper, the author reinforces periodontal disease treatment as a critical checkpoint for women attempting to conceive [15]. Researchers believe that if such treatment happens already in pregnancy, it is perhaps “too late” to prevent any adverse events. The intervention should commence early enough to favor implantation and improve pregnancy outcomes.

Two experimental studies pointed out the infertility problem as secondary outcomes in rodents challenged with periodontitis [16,17]. Despite the different models of experimentally induced periodontitis, both studies found significant lower fecundity rates in the periodontitis groups. It is known that experimental animal studies are at a lower level of evidence, compared to epidemiological studies, but they are the ones that enable mechanism-based reasoning investigations [12].

One of them, also investigated whether periodontitis-induced in rats, similar to a human generalized periodontitis, could increase systemic levels of inflammation, measured by serum levels of cytokines. Although the results were not statistically significant, the pro-inflammatory cytokine IL-1 α [18], was augmented, and the anti-inflammatory cytokine IL-10 [19], was diminished, in the serum of periodontitis animals, compared to healthy ones. Those results reinforce the idea of Periodontal Medicine, when periodontitis is stated as a possible inducer of systemic inflammation and thus systemic diseases trigger.

Biological plausibility of the possible association between periodontitis and infertility

Usually experimental studies are the study types that enable researchers to elucidate the biological mechanism for an association between two conditions, the biological plausibility. To the present moment, no experimental study was conducted to investigate the mechanism-based reasoning linking periodontitis and infertility. The two experimental studies conducted that found such association had infertility as a secondary outcome [16,17]. One of them [17], in the discussion section, exposes two possible biological explanations. As periodontitis causes a systemic inflammation (pointed out in the study results section by the systemic rise of pro-inflammatory cytokines and decrease of anti-inflammatory cytokines) that could interfere with fertility, possibly due to: a) preventing ovulation; b) preventing implantation of the embryo or not sustaining its implantation. It has been demonstrated that cytokines from IL-1 family inhibit the hypothalamic-pituitary-gonadal axis, reducing the gonadotrophin-releasing hormone and luteinizing hormone levels, leading to ovulation failure [20-22]. Also, the progesterone production, essential to successful embryo implantation, is modulated by growth factors and cytokines as IL-1 [23-25]. Likewise, it has been demonstrated that cytokines as TNF- α , IL-1 β , and IL-6 are involved in the regulation of the synthesis, release and metabolism of endometrial prostaglandin F $_2\alpha$ to protect corpus luteum during early pregnancy [26].

Discussion

This evidence-based 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 discerning 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.

Infertility is known as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after at least 12 months of regular unprotected sexual intercourse [27]. Documenting infertility cases could be an intricate process since various continuous

exposures are related to the risk of developing the problem [28]. It is arduous to measure the risk exposures that harm pregnancy over a period of years. Data on marital status, abstinence, coital frequency and timing, contraceptive use, and the partner's presence or absence should be under consideration [28].

Periodontal diseases are also multifactorial, presenting many risk factors and indicators as oral biofilm composition, smoking, diabetes, cardiovascular disease, drug-induced disorders, stress, obesity, osteoporosis, hematological disorders, host response, female hormonal alterations, pregnancy, age, sex, socioeconomic status, education, race, and genetic profile [29-31]. Also, in the literature, many different periodontal diseases definitions have been used in epidemiologic studies [31,32], and the adoption of uniform criteria for those investigations has already been suggested [31], but the comparison among them is still a challenge.

Therefore, conducting epidemiological studies evaluating the association between periodontal diseases and infertility is defiant and require large population samples, ideally restricted inclusion criteria and multivariate analyses to control, as best as possible, the many confounding factors for both conditions.

Meanwhile, experimental animal model studies, with an adequate reproduction model of periodontitis, could be carried out to investigate the biological plausibility of that possible association. The substantial benefit of experimental models is the ability to control the highest number of variables potentially affecting the outcomes studied [17].

In this review, we focused on the women infertility. The onus of infertility in most societies is placed on the woman, and overall, women who have never had a child or are currently childless are more likely to be divorced or separated [28]. When attempting to conceive, patients could be oriented to have a dental check-up as advised to smoking discontinuation, weight loss, and folate supplementation for example [10]. Regardless of the possible association between periodontal diseases and infertility or adverse pregnancy outcomes, the first ones are oral infectious diseases and must always be prevented or treated. So, maintaining general and oral health in all individuals is a common goal for physicians and dentists.

It is known that incorporating oral health into general health agenda is crucial for optimal health and general wellbeing [33]. Therefore, women trying to conceive should ensure that they are in the best possible health, which will be achievable through an effective multidisciplinary teamwork.

Conclusion

As periodontal disease and infertility are public health problems that globally affect patients, it must be screened and prevented. The health professionals should be attentive and cautious about providing their patients a complete evaluation, always seeking for a multidisciplinary teamwork.

References

1. Van Dyke TE, van Winkelhoff AJ (2013) Infection and inflammatory mechanisms. *J Periodontol* 84: S1-7.

2. Williams RC, Offenbacher S (2000) Periodontal medicine: the emergence of a new branch of periodontology. *Periodontol* 23: 9-12.
3. Kinane DF (1998) Periodontal diseases' contributions to cardiovascular disease: an overview of potential mechanisms. *Ann Periodontol* 3: 142-150.
4. Artese HP, Sousa CO, Luiz RR, Sansone C, Torres MC (2010) Effect of non-surgical periodontal treatment on chronic kidney disease patients. *Braz Oral Res* 24: 449-454.
5. Scannapieco FA, Mylotte JM (1996) Relationships between periodontal disease and bacterial pneumonia. *J Periodontol* 67: 1114-1122.
6. Riviere GR, Riviere KH, Smith KS (2002) Molecular and immunological evidence of oral *Treponema* in the human brain and their association with Alzheimer's disease. *Oral Microbiol Immunol* 17: 113-118.
7. Fogacci MF, Vettore MV, Leao ATT (2011) The Effect of Periodontal Therapy on Preterm Low Birth Weight A Meta-Analysis. *Obstetrics and Gynecology* 117: 153-165.
8. Rodrigues M, Barbirato D, Luiz RR, Scharfstein J, Salles GF, et al. (2016) Effect of antihypertensive therapy with angiotensin-converting enzyme inhibitors on chronic periodontitis: a case-control study. *Oral Dis* 22: 791-796.
9. Fogacci MF, Leão A, Vettore MV, Sheiham A, Radnai M, et al. (2010) Periodontal treatment completed before the 35th week of pregnancy appeared to have a beneficial effect on birthweight and time of delivery. Letter to the editor. *J Dent Res* 89: 101.
10. Hart R, Doherty DA, Pennell CE, Newnham IA, Newnham JP (2012) Periodontal disease: a potential modifiable risk factor limiting conception. *Hum Reprod* 27: 1332-1342.
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 4:1.
12. Howick J, Chalmers I, Glasziou P, et al. (2011) *The Oxford Levels of Evidence* 2.
13. Nwhator S, Opeodu O, Ayanbadejo P, Umeizudike K, Olamijulo J, et al. (2014) Could periodontitis affect time to conception? *Ann Med Health Sci Res* 4: 817-822.
14. Nwhator SO, Umeizudike KA, Samuel TA, Soroye MO, Umeizudike TI (2013) Periodontitis & sub-fertility; opinions and practices of Nigerian specialists. *West Afr J Med* 32: 267-271.
15. Hart R (2012) 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)* 8: 229-230.
16. Arce RM, Barros SP, Wacker B, Peters B, Moss K, et al. (2009) Increased TLR4 expression in murine placentas after oral infection with periodontal pathogens. *Placenta* 30: 156-162.
17. Fogacci MF, Barbirato DS, Amaral CS, da Silva PG, Coelho Mde O, et al. (2016) No Association Between Periodontitis, Preterm Birth or Intrauterine Grow Restriction: Experimental Study in Wistar Rats. *Am J Obstet Gynecol* 214: 749.e1-749.e11.
18. Luheshi NM, Rothwell NJ, Brough D (2009) Dual functionality of interleukin-1 family cytokines: implications for anti-interleukin-1 therapy. *Br J Pharmacol* 157: 1318-1329.
19. Couper KN, Blount DG, Riley EM (2008) IL-10: the master regulator of immunity to infection. *J Immunol* 180: 5771-5777.
20. Donesky BW, Dias de Moura M, Tedeschi C, Hurwitz A, Adashi EY, et al. (1998) Interleukin-1beta inhibits steroidogenic bioactivity in cultured rat ovarian granulosa cells by stimulation of progesterone degradation and inhibition of estrogen formation. *Biol Reprod* 58: 1108-1116.
21. Martoriati A1, Gérard N (2003) Interleukin-1 (IL-1) system gene expression in granulosa cells: kinetics during terminal preovulatory follicle maturation in the mare. *Reprod Biol Endocrinol* 1: 42.



22. Sirivelu MP, Shin AC, Perez GI, MohanKumar PS, MohanKumar SM (2009) Effect of L-dopa on interleukin-1 beta-induced suppression of luteinizing hormone secretion in intact female rats. *Hum Reprod* 24: 718-725.
23. Kohen P, Castro A, Caballero-Campo P, Castro O, Vega M, et al. (1999) Interleukin-1beta (IL-1beta) is a modulator of human luteal cell steroidogenesis: localization of the IL type I system in the corpus luteum. *J Clin Endocrinol Metab* 84: 4239-4245.
24. Terranova PF, Rice VM (1997) Review: cytokine involvement in ovarian processes. *Am J Reprod Immunol* 37: 50-63.
25. Zmijewska A, Franczak A, Kotwica G (2012) Role of interleukin-1 α in the regulation of porcine corpora lutea during the late luteal phase of the cycle and during pregnancy. *Acta Vet Hung* 60: 395-407.
26. Franczak A, Zmijewska A, Kurowicka B, Wojciechowicz B, Petroff BK, et al. (2012) The effect of tumor necrosis factor α (TNF α), interleukin 1 β (IL1 β) and interleukin 6 (IL6) on endometrial PGF2 α synthesis, metabolism and release in early-pregnant pigs. *Theriogenology* 77: 155-165.
27. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, et al. (2009) International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Fertil Steril* 92: 1520-1524.
28. Rutstein SO, Shah IHH (2004) Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, Maryland, USA: ORC Macro and the World Health Organization, 2004.
29. AlJehani YA (2014) Risk factors of periodontal disease: review of the literature. *Int J Dent* 2014: 182513.
30. Page RC, Kornman KS (2000) The pathogenesis of human periodontitis: an introduction. *Periodontol* 1997: 14: 9-11.
31. Borrell LN, Papapanou PN (2005) Analytical epidemiology of periodontitis. *J Clin Periodontol* 32: 132-158.
32. Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ (2008) Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol* 35: 385-397.
33. Jin LJ, Lamster IB, Greenspan JS, Pitts NB, Scully C, et al. (2015) Global burden of oral diseases: emerging concepts, management and interplay with systemic health. *Oral Dis* 22: 609-619.

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