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Evidence based comprehensive assessment on poor oral health and infertility: A rationally approached literature review

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Abstract
Literature has well evidenced that several pioneer workers had extensively evaluated the interrelationship between poor oral health and infertility. Periodontal diseases are usually triggered by a pathogenic biofilm with a susceptible host. Nevertheless, periodontitis is one of the most common chronic inflammatory oral diseases, most likely associated with the common systemic diseases and reproductive dilemmas for instance preterm birth, low birth weight, fetal growth restriction, preeclampsia and perinatal mortality. In the Indian scenario, it has been observed that fertility dilemmas are commonly associated with cost burdens, comprising a crisis in families. Such issues are frequently seen to be ended as marital conflicts, leading to divorce. Many of the imperative studies have shown a clear-cut association between oral infections and reduced fertility. Therefore keeping all these intermingling facts in mind, this review literature has been comprehensively attempted to genuinely assess the interrelations between poor oral health/ periodontitis and infertility.

Keywords: periodontal diseases, IVF, infertility, oral health, sterility

Introduction
As per documentations of the International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization (WHO), infertility is a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Furthermore, infertility is also identified as a disease of the reproductive system which can be defined as failure to achieve a clinical pregnancy after at least 12 months of regular unprotected sexual intercourse. Oral diseases and most importantly 'Periodontitis' has their well-established association with several biologic systems as cardiac, urinary, pulmonary, nervous and reproductive, lymphatic and endocrine [2-4]. Periodontal diseases are frequently having multifactorial origin. Periodontal diseases are also representing many risk factors and indicators such as dental plaque concerto, smoking habit, obesity induced diabetes, cardiac disease, immune linked disorders, anxiety, osteoporosis, blood dyscrasias, host based outcomes, female endocrinal upshots, pregnancy, age, sex, socioeconomic status, education, race, and genetic profile [5-7]. In the field of gynecology, inflammation has an imperative role and effect on ovaries, uterus, and embryo and implantation procedures. Furthermore, few oral commensally residing bacteria can stimulate placental inflammation and associated tissue hyperplasia. Conversely, inflammatory cytokines may have a harmful effect on sperm production. Inflammation process is also influenced by the changing levels of the oxidative stress. This phenomenon is largely resulting into 'impair sperm function'. Deleterious processes including oxidative stress usually damages sperm DNA, and finally resulting into 'sperm apoptosis (programmed cell death)' [8-10]. In the recent past, we have observed significant increase in documenting and publishing infertility cases. They were primarily considered and focused on infertility as influenced by the marital status, abstinence, coital frequency and timing, contraceptive use, and the partner's presence or absence should be under consideration. Literature evidence has also shown a possible and crucial role of oral diseases in infertility cases [11-13]. Therefore, considering all these intermingling facts, this review literature has been comprehensively attempted to genuinely assess the interrelations between poor oral health and infertility.

Literature Exploration Methodology
Real execution of any biomedical research without using internet is almost impracticable in the present scenario. Internet offers a number of internet-based tools/apps that augment the retrieval of biomedical information. Few of the reputed internet based popular search engines, scholarly search bibliographic databases and textbooks were searched until Feb 2019 using MeSH (Medical Subject Headings) based keywords such as "periodontal diseases", "infertility", "reproductive sterility", "oral health". Few combinations were also searched like (a) "infertility + periodontitis" (b) "infertility + oral disease" (c) "infertility + gingival disease" (d) "infertility + oral infection". They were searched in prominent bibliographic databases (PubMed, PubMed Central, Medline Plus, Cochrane, Medknow, Ebsco, Science Direct, Hinari, WebMD, IndMed, Embase). The search was limited to original researches, reviews, systematic researches and meta-analyses in various medical journals published over the last 40 years in English language only. A total of 44 relevant articles were recognized however after inspecting the content, keywords and abstracts, this number was finally reduced to 27 papers. The explored data were segregated and studied according to their relevance, credence and year of publication. This was also done to ensure chronological collection of data so as to maximize the result accuracies. Authors have decided to perform this review since review studies are outstandingly valuable and

they also explore comprehensive recommendations regarding clinical practices and evidence based decision makings. Additionally, review studies also provide a wide range of data with enhanced clarification and understanding.

Oral Health and Infertility: A Systematic Literature View Point

Prior to 1978, women without physiologic fallopian tubes were mostly considered to be sterile by their doctors. As a proven fact, at least one functional fallopian tube is essential for natural fertilization of an oocyte by sperm in vivo. History has evidenced that the birth of Louise Brown in 1978 was the zenith of decades of biomedical research in reproductive medicine. Since then, a plenty of breakthroughs in both clinical medicine and basic science have been seen. This has created a medical boom amongst infertile couples by dramatically increasing their chance to have a baby. One of the main etiologies of male infertility is anomaly of endocrinal or testicular function. Likewise, female infertility is commonly allied with the ovulation problems, diseases of the cervical mucosa, endometriosis, endometrial adhesions and other morphological dilemmas of the fallopian tubes. Although, literature search has not revealed extensive works on relation between poor periodontal health and fertility issues. Periodontal diseases are usually triggered by gram-negative anaerobic bacteria and these bacteria are competent of generating numerous mediators of inflammation. Some of the common mediators are prostaglandins [PG], interleukins [IL], lipopolysaccharides, and endotoxins. These gram-negative anaerobic bacteria and their metabolic byproducts can have easy entry into the circulatory system. After getting entered into the blood circulation, mediators of inflammation cause a risk to the health of the mother. Even they can cross the placental barrier and ultimately cause fetal toxicity. Over past few decades, various studies have been done on the assessment of oral health/Periodontitis and infertility. In 2015 Fogacci *et al*. done a study on rats wherein they studied 13 periodontally healthy control group and 27 induced ligature periodontitis group. They found that ligature-induced periodontitis did not result in adverse pregnancy outcomes. However that noticed that infertility was a secondary outcome found in the periodontitis group. They stated that periodontitis usually results into a systemic inflammation (they highlighted it in their results section by the systemic rise of pro-inflammatory cytokines and decrease of anti-inflammatory cytokines). Therefore, periodontitis could interfere with fertility, possibly due to: a) preventing ovulation; b) preventing implantation of the embryo or not sustaining its implantation. They have also showed that cytokines from IL-1 group slow down the hypothalamic-pituitary-gonadal axis, dipping the gonadotrophin releasing hormone and luteinizing hormone levels, ultimately leading to ovulation failure [14]. Nwhator *et al*. in 2014 performed a case-control study on 70 pregnant and 58 non-pregnant. What all they committed were: periodontal examination: oral hygiene index score, the community periodontal index and the periodontitis risk score measurement using matrix metalloproteinase. They reported that there were greater odds of conception within one year for the subgroup with good oral hygiene. The study strongly recommends the need for periodontal examination in women trying to conceive [15]. Nwhator *et al.* in 2013 done a study on 111 specialists and 8 general practitioners those participated in the internet based survey on infertility and oral health. There results illustrated that 75 professionals were managing sub-fertility patients and only one practitioner requested a periodontal/dental consultation for the subfertility patient under care [16]. Franczak and coworkers demonstrated that cytokines as TNF-α, IL-1β, and IL-6 are involved in the regulation of the synthesis, release and metabolism of endometrial prostaglandin F2α to protect corpus luteum during early pregnancy [17]. Donesky and colleagues 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 [18]. In 2012, Hart and co researchers did a study on 1956 mid-pregnant women, 516 with periodontal pockets ≥ 4 mm at 12 or more sites in fully erupted teeth, 1439 women without periodontal disease. They also suggested that periodontal disease might affect fertility, increasing the time to conception in 2 months, on average, but only statistically significant in the non-Caucasian [19]. Oguz and coworkers also did a similar study and showed that a significant relationship between chronic periodontitis and erectile dysfunction in young adults within the age range of 30-40 years. According to the results of logistic regression analysis in the mentioned study, a significant association was observed between this disability and severity of chronic Periodontitis [20]. Francois and colleagues estimated the relationship between low birth weight and subsequent male subfertility in future, which could be resulted from possible prenatal growth restrictions [21]. However, Ozturk *et al.* showed that, the pathophysiological mechanism governing this association has remained unknown. Quite the opposite, Ozturk and coworkers recognized no significant difference between the samples of the case and control groups, suggesting that low birth weight possibly had no impact on male fertility later in life [22]. Kavoussi and colleagues did a contrasting study and performed the intricate evaluation of collected data from 4,136 women (aged 18-50 years). They suggested a possible association between endometriosis (a potential cause of infertility) and periodontal diseases. According to the results of their research, while multifactorial endometriosis could increase due to the immune response to infectious agents, the potential underlying relationship between periodontitis and endometriosis may be a generalized, global immune deregulation. Each disease is characterized as a chronic, inflammatory disorder associated with an altered immune response [23]. Weiss *et al.* and Kim *et al.* showed that in gynecology, inflammation has a significant impact on ovaries, uterus, embryo and implantation. A remote, low grade oral infection may trigger inflammation of the maternal-fetal unit similar to bacterial vaginosis. Additionally, some oral bacteria can induce placental inflammation and decidual hyperplasia [24-25]. Therefore, on the basis of these inferences one can recommend that, women who intend to become pregnant must be ensured of their oral health and consider oral and dental examinations in addition to checking different factors involved in their general health. Because most oral inflammations (periodontitis) are curable, all women must be promoted to have a dental checkup before trying to conceive [26-27]. Considering the fact that seminal factors might be improved in men after curing of periodontitis, it is advisable that dental examinations be also done on males. Right

identification of such interrelationship between oral health and diminished fertility by gynecologists and dentists can contribute to the prevention of deleterious adverse effects of such dilemmas.

Conclusion

Many of the studied pioneer workers have shown that oral hygiene is an imperative component of general health and also a contributing factor for enhanced sexual health. This paper clearly indicates interrelation of oral health/ periodontitis and infertility. Poor oral health has been shown to have deleterious effects on overall fertility and other related parameters. Prevention of oral inflammation and regular dental visits by men and women, particularly prior to conceiving, could be promoted to enhance reproductive ability. Additionally, the health professionals must be having serious attitude and approaches while managing such clinical circumstances.

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