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Research Article

Periodontal Disease, Infertility Treatment and *In Vitro* Fertilization (IVF)

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Abstract

In the last years, research interest has focused on the possible role of maternal periodontitis in the achievement of a pregnancy, as well as the possible role of paternal periodontitis in the success of medication administered for the treatment of infertility. The purpose of this publication is the presentation of the limited number of research data that highlight the relationship between maternal/paternal periodontitis and the effectiveness of fertility treatment.

From the results of the small number of studies published to this day, mainly conducted in small population samples, it can be shown, that periodontal disease, especially periodontitis, could, as a chronic bacterial infection, affect the effort to treat fertility problems. Nevertheless, the confirmation of this effect requires further in-depth research. Until then, one could point out that periodontal disease should be treated upon diagnosis, even before addressing the infertility problem.

Keywords: Periodontal disease; Fertility; Infertility; IVF; Gestation

Introduction

From the moment of conception until birth, the fetus is placed under the influence of various stimuli, which derive primarily from various pathological conditions or harmful habits of the expectant mother. From the existing research it has been fully established that many of these conditions or habits may affect the oral health of the fetus, as this is determined in the early months of the pregnancy.

Today, there are clear documented research data, according to which various viral infections or febrile diseases can increase the risk of developmental defects, such as cleft palate and enamel hypoplasia, predisposing to caries in both the deciduous and the permanent dentition [1,2]. Furthermore, serious eating disorders during the pregnancy, as well as deficiencies of vitamins A, B, C and folic acid may be associated with the occurrence of enamel hypoplasia defects, deceleration of the time of tooth eruption and occlusal disorders [3]. Folate deficiency, in particular, which can occur after alcohol consumption or intake of antidepressants and anti-epileptics during the pregnancy, can be correlated with increased risk of conformation anomalies such as cleft palate, lip palate and maxillary hypoplasia [4,5]. Also, the intake of tetracyclines, during the 2nd and 3rd trimester, can cause staining of the deciduous teeth [6], whereas the smoking habits of a pregnant woman, especially during the 1st trimester of the pregnancy pose an increased risk for the appearance of lip palate, cleft lip palate or cleft palate [7].

Relatively recently, after over 15 years of extensive clinical research, it had been estimated that maternal periodontitis can constitute a potential risk factor in the outcome of the pregnancy, by increasing the risk of premature or low birth weight or premature and low birth weight newborns or causing other implications such as preeclampsia, perinatal mortality or growth retardation of the fetus [8-15]. Therefore, the potential "benefit" that can occur after the treatment of the maternal periodontal disease with non-surgical techniques during the pregnancy has also been investigated [16-21]. However, in both research fields, the findings have been conflicting and possible associations have not been adequately documented. Even after meta-analysis of the existing research data, maternal periodontitis cannot be undoubtedly classified among the risk factors for preterm or low birth weight [22-31]. Vice versa, it cannot be positively confirmed that periodontal therapy could contribute in the prevention of those births [32-39].

In the last years, the scientific interest had also been focused on the role of maternal periodontitis in the achievement of a pregnancy, which could occur, either normally after the administration of appropriate medication in order to treat infertility, or after planned sexual contact or implementation of other techniques such as IVF.

The purpose of this publication is the presentation of the limited number of research data that focus on the possible relationship between maternal and/or paternal periodontitis and the effectiveness of the infertility treatment and thus the achievement of a pregnancy. Furthermore, it is also highlighting the findings of two recent clinical studies presenting a possible correlation of the periodontal maternal status to the effectiveness of an *In Vitro* Fertilization treatment.

Maternal Periodontitis and Pregnancy

It is a fact, that the binding ability of the sexual hormones exists both in the gingival tissues as well as the saliva, an ability attributed to their specific receptors [40-43]. The binding of these hormones becomes particularly important in the co-existence of gingival inflammation, as this guarantees their metabolic ability, to an extent greater than in periodontal health [44,45]. Consequences of this initial binding and subsequent metabolism of these hormones are significant changes in the microcirculation and the permeability of the gingival capillary vessels [46], the suppression of the cell-mediated immunity [47] and the qualitative and quantitative change of the subgingival microbial flora [48,49]. All these microbiological, vascular, cellular and immunological changes, mainly attributed to the increase of the concentration of sexual hormones during a pregnancy, could influence pre-existing periodontal disease progression, although the true interaction's mechanism is still not determined [50].

Periodontal disease and particularly periodontitis is a chronic bacterial infection, and belongs, as well as various other acute or sub-clinical infections, especially of the urogenital system, appendicitis and

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pneumonia, to the category of those infections that may be considered as potential risk factors that adversely affect the outcome of the pregnancy [51,52].

In particular, the effect of maternal periodontitis in the progression and outcome of a pregnancy can be interpreted with the help of two cases that have been adequately documented [53]. The first case concerns the ability of the endotoxins of the Gram-negative periodontal bacteria to cross the placenta, through the blood circulation and decisively affect the development of the fetus, as evidenced by the identification of bacteria associated to periodontitis in cultures of amniotic fluid [54-57]. The second case relates to the treatment of maternal bacteremia with the overproduction of pre-inflammatory cytokines and enhances of the immune response of the thermal shock proteins which were shown by the detection of inflammatory mediators in high concentrations in the amniotic fluid of women who delivered preterm [58].

Regarding the effect of maternal periodontitis in the achievement of a pregnancy, it has been interpreted mainly through the bacteremia, which can initially occur in the uterus through the endotoxins in the blood circulation, such as lipopolysaccharides and other bacterial products of Gram-negative periodontal bacteria. Maternal bacteremia activates the immune mechanism, triggering the overproduction of preinflammatory cytokines and prostaglandins. This is strongly supported also by the findings of various studies, performed by gynecologists, identifying a significant relationship between a former maternal, even subclinical infection and a failed attempt of IVF [59-61].

The fact that there is still a significant failure rate in the various methods applied to treat infertility [62], despite the progress of knowledge and techniques being used, has recently triggered further research regarding the role of maternal periodontitis in the achievement of a pregnancy. The question formulated was whether the bacteremia, which is present in the uterine cavity due to the periodontal disease present in the oral cavity, may significantly influence the effectiveness of hormonal therapy, administered during the treatment of infertility, in order to achieve a pregnancy. This gestation can occur either during a normal reproductive cycle after a planned sexual contact or after an IVF.

A search of the relative literature revealed limited number of studies, either exploring the influence of the hormonal treatment on periodontal tissues or a possible relationship between the maternal periodontal disease and the efficacy of the infertility treatment, which is defined by a successful ovarian stimulation and the development of multiple oocytes.

Maternal or Paternal Periodontitis and Infertility

The term "infertility" is used to define the failure of a woman to conceive, after a year of effort and unprotected and without the use of contraceptives intercourse. Typically, 80-85% of pregnant women conceive normally within a year, while 10-15% of women experience infertility problems [63]. Infertility is directly correlated with age, since only 4% of the couples between 20-30 years experience infertility problems, while this figure increases significantly, reaching about 20% at the age of 30-40 years. In the total of infertility problems and hence the impossibility of couples to bear children, it was found that male infertility is responsible for 40% of the cases female infertility for another 40%, while for the remaining 20% of the cases both partners are responsible [64].

The main causes of male infertility may be associated with the endocrine function or testicular abnormalities. Correspondingly, female infertility may be caused by disorders associated with the ovarian function and therefore ovulation, disorders or dysfunction of the cervical mucus, endometriosis, endometrial and endopelvic adhesions, conditions associated with the potency of the fallopian tubes, or pathological anatomy of the uterus, etc.

The question which arises is whether the fertility of a woman or a man may be influenced by their oral and in particular their periodontal condition, since the periodontal disease, as a chronic bacterial infection, may be associated directly or indirectly with the presence or establishment of other subclinical infections, which form the causes of infertility [51,52]. The answer to this question is difficult, since there are limited research data, that correlate periodontal disease and periodontitis in particular to the possibility of achieving a pregnancy, in women with infertility problems [65,66] or in situations of men infertility [67,68].

The first information regarding a possible connection between a man's fertility and his oral health derive from Bieniek and Riedel [67], who designed a study in order to investigate whether a dental infection caused by various bacteria, spreading through the blood circulation, can potentially lead to infertility. This study involved 36 men with bacteriospermia, resistant after the administration of an antibiotic therapy, who received a dental examination, through which a high rate of dental infection had been detected. These individuals were separated into two equal groups of 18 people. In the experimental group, all the necessary dental treatments were made, in order to restore full oral health and to successfully eliminate any foci of infection. Six months later, the new spermιograms of the $^{2}/_{3}$ of the participants of the experimental group were found to be sterile, while parameters such as mobility, density or morphology of sperm were clearly improved. The conclusions of this study highlighted for the first time the importance of oral health for people with fertility problems, the solution of which in many cases should not be limited to the prescription of medication.

Many years later, the relationship of infertility and periodontal disease was re-explored in a cross-sectional survey study of Kavoussi et al. [65]. In this study, the researchers investigated the relationship between periodontal disease and endometriosis, using the data of 4,136 women, aged 18-50 years, who were involved in a large multicenter study of the National Health and Nutrition Examination Survey in the years 1999-2004. The recording of endometriosis was made by the use of self-report data, whereas the periodontal disease was recorded using clinical examination data, involving pocket depth, loss of clinical attachment and bleeding on probing.

They defined as gingivitis the situation in which the clinical findings related to gingival bleeding in one or more quadrants or even surfaces and as periodontitis the situation in which in one or more teeth or surfaces a pocket depth ≥ 4 mm could be detected and clinical loss of attachment ≥ 2 mm. Based on their periodontal condition, the women were classified initially in those with a healthy periodontium (1,466 subjects) and those with periodontal disease (1,865 subjects) and subsequently, those with gingivitis (1,154 subjects), those with periodontitis (168 subjects) and those with both gingivitis and periodontitis (543 subjects). It is worth mentioning, that all data have been processed for 2,664 and not 4,136 women, mainly due to lack of complete data or responses to the questionnaire distributed. This study found that women who reported existence of endometriosis in their medical history, had a significantly higher percentage (57%) of gingivitis and periodontitis compared to those women without periodontal disease (a-OR=1.57 {95% CI:1.06-2.33}). A similar finding could not be applied for women with gingivitis (1,154 people, a-OR=1.26 {95% CI:0.83-1.91}) or periodontitis (168 people, a-OR=0.42 {95% CI:0.13-1.34}). These data were determined after simulation of all those factors that could affect the outcome.

Further research information was obtained three years later, from the study of Hart et al. [66] in 3,737 pregnant women in the context of a multicenter study (Smile study) in Australia. All women who had undergone fertility treatment were excluded, ultimately leading to the evaluation of data of 3,416 women 1,014 (29.7%) of those were found to have periodontitis that was determined by pocket depth of ≥ 4 mm on at least 12 teeth. It was found that the period of time needed to achieve a pregnancy was greater than 12 months in 146 women, who suffered in a larger and statistically significant percentage of periodontitis (34.9% vs. 25.7%, p=0.015). It was also shown that the time to achieve the desired gestation was two months longer in women who had periodontitis (7.1 months {95% CI:5.7-8.6}) corresponding to those who had no periodontitis (5.0 months {95% CI:4.4-5.5}). Given that periodontitis in Caucasian women were at a rate of 23.8% and non-Caucasians 41.4%, it was still found that the period of 12 months and longer in order to achieve a pregnancy was significantly increased only in non-Caucasian (13.9% vs. 6,2%, OR=2.88 {95% CI:1.62-5.12}; p<0.001) and not in Caucasian women (8.6% vs. 6.2%; OR=1.15 {95% CI: 0.74-1.79}; p=0.534).

A year before, Klinger et al. [68] published an interesting study, which sought a possible correlation between different parameters of fertility and the periodontal status of men, who participated in a program of *In Vitro* fertilization (IVF, *In Vitro* Fertilization) as partners. The study population consisted of 75 men attending the clinic for sperm analysis before homologue semen insemination or IVF. The quality of sperm was assessed according to WHO criteria. On the same day, patients received a clinical periodontal examination. Upon clinical examination, the number of extracted teeth, the plaque and gingival index, the number of mobile teeth, the pocket depth and loss of clinical attachment were recorded. The participants were categorized as patients with gingivitis when at least two surfaces had gingival index 1, 2 or 3, but no clinical attachment loss (30 subjects, 40%) and patients with periodontitis, when at least two sites had pocket depth ≥ 4 mm and simultaneously, bleeding on probing (36 subjects, 68%). The findings of this study identified a trend of correlation between poor sperm mobility and the number of sites with deep pockets (2 or 3 surfaces with deep pockets ≥ 3 mm), which was not statistically significant. A statistically significant difference regarding the sperm mobility could be determined among individuals with clinical attachment loss >1 mm in at least one site and individuals without similar clinical data (p=0.03).

Maternal Periodontitis and Infertility Medication Treatment

The basic treatment of the reproductive function in cases of possible infertility is a scheduled sexual contact during a normal reproductive cycle, initially without and then with the administration of the appropriate medication [69].

The administration of clomiphene citrate on the beginning of the genetic cycle, usually from the 2nd up to the 6th day is usually selected as the first solution, due to the drug's anti-estrogenic action [70,71]. Alternatively, gonadotropin can also be administered intramuscularly or subcutaneously in small doses, in order to enhance follicular development. The administration of these drugs has minimal side effects, the risk for ovarian hyperstimulation is rare, with the exception of those cases of polycystic ovarian syndrome, and the possibility of multiple gestations is very small. This method is applied in cases of ovulation disorders and dysfunctions or disorders of the cervical mucus and is usually implemented in order to achieve multiple follicular development and ovulation induction.

A fundamental question that rises is whether the administration of drugs to restore ovulation problems can affect an already existing periodontal condition, or deteriorate it. Furthermore, could this contribute indirectly and in combination with the presence of periodontal disease in the manifestation of maternal bacteremia, thus limiting the possibility of achieving a pregnancy? The answer to this question has barely been explored either individually, i.e. the administration of medication and achievement of a pregnancy naturally or in the context of IVF in order to achieve ovarian stimulation and receive multiple eggs.

The only reference regarding the administration of medication in order to treat ovulation problems and its impact on the gingival tissues was made in a study of Haytac et al. [72]. The treatment involved the administration of clomiphene citrate (CC) alone or in combination with pituitary hormones, which was the follicle-stimulating hormone (FSH) or human menopausal gonadotropin (HMG). By applying specific criteria four experimental groups (18 women receiving CC for a period of less or at least three cycles, 16 women receiving CC for a period of more than three cycles, 21 women receiving CC + FSH and 24 women receiving CC + HMG) and one control group (20 women) were established, a categorization also supported by an assimilation of various factors such as the age, education level and oral hygiene habits.

The findings of this study showed statistically significant differences in all three experimental groups compared to the control group, such as increase in gingival inflammation both in women treated with CC (p<0.01) and in women receiving combined CC + FSH (p<0.001) or CC + HMG (p<0.001). There was also, statistically significant differences between experimental and control group in both bleeding on probing and gingival fluid volume (p<0.001). In particular, the value of bleeding on probing was much higher in women receiving combined CC + HMG (23.08% ± 8.16%) or CC + FSH (22.85% ± 8.18%) or only CC for more than three months (21.56% ± 6.63%) compared to that of the control (10.15% ± 7.05%). It was also found that these clinical findings correlated, as to their seriousness, to the duration of the medication, which was at least three months. These changes of clinical indicators were identified despite the fact that there were no differences in the level of oral hygiene, as monitored with the plaque index. The conclusions of this study showed the inflammatory burden of gingival tissue from the prescription of hormonal ovarian stimulation treatment, an option that is indeed the most common method for the treatment of ovulation problems. However, this study did not determine whether the inflammatory burden was associated with diseased or healthy periodontium, since there is no such distinction in the experimental groups, and respectively, in the control group. Also, it is not being indicated in which cases the therapy was associated to a pregnancy and whether this achievement was combined with the periodontal status initially, or subsequently, the periodontal treatment. Thus, based on the findings of this study, the inflammatory burden of gingival tissue and the deterioration of periodontal infection is the main conclusion made. An infection that may restrict the achievement of a pregnancy, especially when the maternal periodontal disease preexisted and when others, possible multiple drug efforts with similar hormonal preparations have already occurred.

Parental Periodontitis and *In Vitro* Fertilization (IVF)

When all efforts of medication treatment in combination with scheduled sexual contact fail, *In Vitro* fertilization (IVF) is usually applied. The application of this technique is decided based on specific criteria, which are mainly the age of the partners, the state of the ovaries or sperm quality [69-73].

The correlation between the success of an IVF program and the

periodontal status of the expectant mother is a rather new field of research with little information, although the existing research data could be characterized as remarkable [74-76].

The evaluation of the potential inflammatory burden of gingival tissues after receiving hormone medication therapy, within an IVF program, was investigated for the first time in the study of Pavlatou [74], which evaluated the effect of this burden on the effectiveness of IVF, at least as to the final number of fertilized eggs implanted in the uterus of these women. More specifically, in this study, 19 women of reproductive age, who had never been involved in a similar IVF program and who had also not received similar hormonal medication or periodontal treatment in the last semester, were selected on strict criteria. The findings of this study determined that at the end of the IVF program, a slight but not significant increase in the mean value of the gingival index (GI, Löe and Silness 1963; p=0.154) was detected, but was not associated with a corresponding change in the value of the index plaque (PlI, Silness and Löe 1964; p=0.911). This increase of the gingival index correlated significantly with the dose of gonadotropin administered (p=0.031) and the final number of fertilized eggs, that were implanted (p=0.038). The conclusions of this study showed that hormones administered as part of an IVF program, seem to affect the gingival tissues, causing an aggravation of inflammation, while this effect appears to affect and the final number of fertilized ova. These data can only be seen as indicative, while forming also a motivation for further detailed investigation. The main drawback of this study was the lack of separation of the women depending on their periodontal condition, apparently due to their small number. It is worth mentioning that in this sample of women, and according to CPITN (Community Periodontal index treatment need), there was only one woman with healthy periodontium, four women with healthy periodontium but in need of instruction in oral hygiene, 7 in need of treatment for gingivitis and 7 in need of non-surgical periodontal treatment.

Ten years later, in her doctoral thesis, Pavlatou [75] investigated the possible effect of the periodontal status of women on the effectiveness of IVF, which was demonstrated by the ability of ovarian stimulation, the development of multiple eggs, the choice of the most suitable embryos for implantation and finally, the achievement and progress of the pregnancy. The subjects were categorized according to their pre-existing periodontal condition (20 subjects with healthy periodontium, 19 with gingivitis and 21 with mainly mild periodontitis) and the examination was focused on the clinical and qualitative or quantitative changes that may occur in the subgingival microbial flora during an IVF. The study involved 60 women of reproductive age, selected based on strict criteria, who have not received any hormonal medication or periodontal therapy for the last 6 months. Findings from the analysis of the clinical data showed that there were no statistically significant differences in the mean value of estradiol (p=0.25), the number of retrieved oocytes (p=0.25) and suitable for implantation embryos (p=0.22), depending on the initial periodontal status of the participants. A statistically significant (p<0.001) increase in the gingival index after completion of the IVF (from 31.9% ± 18.7% to 61.7% ± 23.5%) was observed, which was significantly higher in women with gingivitis (from 37.1% ± 5.7% to 77.6% ± 6.7%), rather than those with periodontitis (from 50.2% ± 7.1% to 77.6% ± 7.4%), or with healthy periodontium (from 7.9% ± 1.2% to 29.8% ± 4.4%). In none of these three groups could it be associated with a corresponding increase in the index plaque. For all women, there was a tendency of correlation of the gingival index before the IVF with the number of oocytes obtained after ovarian stimulation (r=-0.26; p=0.04) and the gingival index after IVF with the number of embryos suitable for implantation (r=-0.28; p=0.03). Furthermore, a tendency of correlation of bleeding on probing after IVF with the number of retrieved oocytes (r=-0.45; p=0.04) and the number of embryos suitable for implantation (r=-0.50; p=0.02) was observed in women with periodontitis [76].

The findings of the microbiological data analysis showed that after completion of the IVF a change in the composition of the subgingival flora could be detected, mainly concerning the group of periodontal pathogens in the total of women (p=0.018) and in particular, women with periodontitis (p=0.00). It was also found that there was a similar change in the group of periodontal pathogens of mild pathogenesis in women with healthy periodontium (p=0.006) and gingivitis (p=0.022). It was also determined that there was a correlation tendency of the estradiol's value with the changes of the physiological flora in all women (r=-0.35; p=0.01). Furthermore, it was determined that in women with healthy periodontium, the composition of the subgingival flora before an IVF (p=0.009) and in particular, the physiological microbial flora (p=0.030) and periodontal pathogens (p=0.030) could be associated with the achievement of a pregnancy. Similarly, it was found that in women with gingivitis, after the IVF, the composition of the physiological microbial flora was related to the estradiol's value (r=-0.55; p=0.019), whereas the composition of the periodontal pathogens was associated to the development of the pregnancy (p=0.031). Finally, in women with periodontitis, a correlation tendency of the total composition of the subgingival flora to the estradiol's value (r=-0.52; p=0.016) was observed before the IVF and in particular of the periodontal pathogens of mild morbidity to the number of received oocytes (r=-0.45; p=0.039) and suitable for implantation eggs (r=-0.53; p=0.01) (Pavlatou 2013). In conclusion, despite the restrictions that existed, such as the small number of women, separated to the individual groups according to their initial periodontal status and including women with mild periodontitis, namely shallow pockets, in the group with periodontitis, this study presents significant findings. As a general conclusion, it should be mentioned, that the maternal periodontal health or disease may be affected by the administration of the hormonal medication therapy before the application of IVF but can also determine the effectiveness of this treatment, even if this is expressed as a correlation tendency.

Conclusions

From the results of the small number of studies published to this day, mainly conducted in small population samples, it can be shown, that periodontal disease could, as a chronic bacterial infection, possibly affect the effectiveness of infertility treatment methods and subsequently, the achievement of a pregnancy. The correlation between the success of an IVF program and the periodontal status of the "expectant mother" is a rather new field of research with little information. Furthermore, the possible effect of the paternal periodontal condition on male fertility and the achievement of a pregnancy remain to be determined, as very few studies have dealt with this topic.

Nevertheless, the confirmation of this effect requires further in-depth research in the years that follow in order to verify the existence of a correlation between maternal periodontitis and the effectiveness of an infertility treatment. The verification of an existing relation would furthermore make the need of periodontal treatment upon diagnosis, even before addressing the problem of infertility, imperative.

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