Periodontal disease and poor obstetrical outcome

G. Carta[1], G. Persia[2], K. Falciglia[1], P. Iovenitti[1]

[1]Department of Surgical Science, University of L'Aquila
Unit of Obstetrics and Gynecology. Avezzano Hospital
[2]Department of Dentistry. "Don Orione" Institute of Avezzano (Italy)

Summary

Maternal infective processes sustained especially by Gram-negative anaerobic bacteria like periodontal disease, during pregnancy, have been demonstrated to perturb the physiologic course of parturition through inflammatory cytokine production, sometimes resulting in preterm labor, preterm premature rupture of membranes and preterm low birth weight. In a matched case-control study, the hypothesis that poor oral health of pregnant women is a risk factor for low birth weight (LBW) was evaluated. Gingival crevicular fluid levels of PGE_2 and IL-1β were measured in order to determine whether mediator levels were related to current pregnancy outcome. Results indicate that GCF-PGE_2 and GCF-IL-1β levels are significantly higher in preterm low birth weight (PLBW) mothers as compared with normal birth weight controls. The data confirm that there is a possible correlation between periodontal problems typical of pregnancy and the occurrence of complications such as preterm low birth weight.

Key words: Periodontal disease; Pregnancy; Complications during pregnancy.

Introduction

Several studies indicate a statistically significant relationship between periodontal disease and poor obstetric outcomes such as preterm low birth weight (PLBW).

Offenbacher *et al.* argue that chronic infective processes prevalently sustained especially by Gram-negative anaerobic bacteria such as periodontal disease, may have a negative effect on the course of pregnancy through proinflammatory cytokine production [1-5].

During pregnancy there is a systematic inclination to periodontal disease due to physiologic hormonal changes. In particular, there is a global rise in anaerobic Gram-negative agents such as F. Nucleatum, T. Denticola, B. Forsythus, A. Actinomycetemcomitans, C. Rectus, E. Corrodens, S. Sputigena, some of which are found in large quantities in women with adverse pregnancy outcome [5, 6]. It is thought that the causal factor of periodontal disease in some pregnant women remains the plaque and tartar accumulation, caused by a poor oral hygiene and a genetic predisposition. Periodontal disease may have a negative influence on pregnancy even if located far from the feto-placental unit. It has been clearly demonstrated that intra-oral manipulation, such as toothbrushing, has the potential to cause Gram-negative bacteremias and that these bacteremias occur more frequently in people with more plaque and gingival inflammation [7].

Anaerobic Gram-negative germs are not able to get through the tissue barrier and live in the aerobic environment of the circulation, whereby the adverse effects on pregnancy are mediated by release of the major components of the bacterial cell wall of Gram-negative cells, the lipopolisaccharide (LPS). The LPS in systemic circulation can bind itself either to serous proteins or to LPS-binding proteins. In the latter occurrence, several kinds of cells such as epithelial cells, endothelial cells, PMN, macrophages could activate themselves and produce inflammatory mediators like PGE_2, IL-1, TNFα [8, 9].

Many studies have suggested that PGE_2 and cytokines such as IL-1 and TNF-α play an important role in the normal physiologic process of parturition as well as in the pathologic prematurity [10-13]. Amniotic fluid levels of PGE_2 rise steadily throughout pregnancy until a critical threshold level is reached to induce labour, cervical dilation and delivery. Romero *et al.* observed elevated levels of PGE_2 as a consistent and reproducible fact of PLWB, even in the absence of clinical or subclinical genitourinary tract infection, and they postulated that the majority of PLBW cases are probably caused by an infection of unknown origin [14]. IL-1β is a potent stimulator of the synthesis of prostaglandins by decidua and amnion and was the first cytokine implicated in the onset of the labor in the presence of infection [15-17].

The purpose of this study was to evaluate the incidence of periodontal disease in the PLBW case versus controls and measure the gingival crevicular fluid level of PGE_2 and IL-1β to determine whether mediator levels were related to current pregnancy outcome.

Materials and Methods

Patient selection

A matched case-control study with a selection ratio of one was performed using 46 cases and 46 controls derived from among 92 mothers who delivered their babies at the Surgical Unit of Avezzano Hospital, during 2001.

Each patient received an appropriate description of the study and informed consent was obtained. Cases were defined as mothers delivering an infant weighing less than 2,500 g and born before 37 weeks' gestational age, as a result of preterm labour or preterm premature rupture of membranes (pPROM) in the actual pregnancy or who had a history of PLWB in the past.

Revised manuscript accepted for publication September 9, 2003

Controls were mothers delivering an infant weighing more than 2,500 g born after 38 weeks' gestation and who had no prior abnormal pregnancy outcome history. Only primiparous cases or controls were considered. Information about current and past obstetric history was obtained from each mother through a personal interview conducted by a trained interviewer. Women with diabetes, asthma, heart disease, glomerulonephritis and hyperthyroidism or those with a history of one of these diseases were excluded.

A detailed profile of known obstetric risk factors was assessed for each patient, including coffee and alcohol consumption, tobacco usage, treatment or diagnosis of bacterial vaginosis, history of bacteriuria, level of prenatal care and weight gain during pregnancy. Oral examinations were performed by the investigator using the World Health Organization criteria [18]. The status of the dentition and the periodontal status of all patients were recorded using the DMFT index (Decayed, Missing, Filled Teeth), an indicator of the total number of teeth that are either decayed, missing due to dental caries or filled as a result of caries, and the CPITN index (Community Periodontal Index of Treatment Needs) that measures periodontal health using five possible scores from 0 to 4, where severe disease is defined as CPITN score 4.

Gingival crevicular fluid samples

Gingival crevicular fluid (GCF) is a transudate that physiologically appears around the neck of the tooth at the gingival margin. In the presence of gingival inflammation, the GCF flow increase and the fluid contains inflammatory mediators diffused from the adjacent inflamed gingival tissue. Four gingival crevicular fluid samples per mediator were taken from each woman within 48 hours from labour. Samples were collected using paper strips and gingival crevicular fluids volumes were determined. Samples were stored in liquid nitrogen and analysed for the quantification of PGE_2 and IL-1β using an ELISA assay kit.

Statistical analysis

The results were analysed by the χ^2 test and Student's t-test where appropriate. Differences in p values < 0.05 were considered statistically significant.

Results

On the basis of the CPITN scores, the periodontal disease status was worse in PLBW mothers than in normal birth weight (NBW) mothers. In fact, in the NBW mothers the prevalence of a CPITN score of 4 was 3%, in agreement with the periodontal disease data from the Adult Dental Health (ADH) Survey, while in the PLBW mothers almost 40% were found to have a CPTIN score of 4. Furthermore, only 10% of the mothers examined were free of any periodontal disease, in contrast to the ADH Survey data which suggest that 27% of the women were classified as CPTIN score 0.

The mean GCF-PGE_2 level was determined for each group. The pooled mean for the control mothers was 55.3 ± 9.8 ng/ml and the mean for the PLBW mothers was 168.7 ± 19.5 ng/ml.

The mean GCF-PGE_2 levels were significantly higher in the case group versus the control group ($p < 0.05$). The mean level for case mothers was more than three times the level noted for control mothers. The mothers with higher GCF-PGE_2 levels had smaller and more premature babies.

For analysis, GCF-IL1β samples were polled. The NBW control group had a mean GCF-IL1β level of 633.7 ± 98.2 ng/ml, while the PLBW case group had a mean GCF-IL1β level of 1723.9 ± 305.1 ng/ml. The mean GCF-ILβ level was higher in cases when compared to controls ($p < 0.05$) (Table 1 and Figure 1).

Discussion

Periodontitis is the result of a delicate balance between microbial plaque organisms and the host response. Changes in the nature of the bacteria and/or the virulence factors they produce, as in pregnancy, may alter the balance between health and disease either by direct effects on the tissues or by the deregulation of the inflammatory response, and so may change the quality or effectiveness of the host defences. A clear role of subject-based and environmental factors on the clinical outcome of the interplay between periodontal bacteria and the host response exhibits an intimate link between oral and systemic health. This has led to examination of the hypothesis that the persistent Gram-negative bacterial challenge and concomitant unregulated or deregulated host response associated with periodontal disease may have consequences that extend beyond the periodontal tissues themselves. Evidence suggests significant associations between periodontal disease and pregnancy complications such as PLBW may be due to inflammatory cytokine production [3]. The proposed link between maternal periodontal disease and PLBW is particularly interesting. First, infections far from the developing fetus

Table 1. — *Mean GCF-PGE_2 and IL-1b levels for NBW and PLBW groups.*

	GCF-PGE_2 (ng/ml ± SE)	GCF-1L1β (ng/ml ± SE)
NBW (n = 46)	55.3 ± 9.8	633.7 ± 98.2
LBW (n = 46)	168.7 ± 19.5	1723.9 ± 305.1

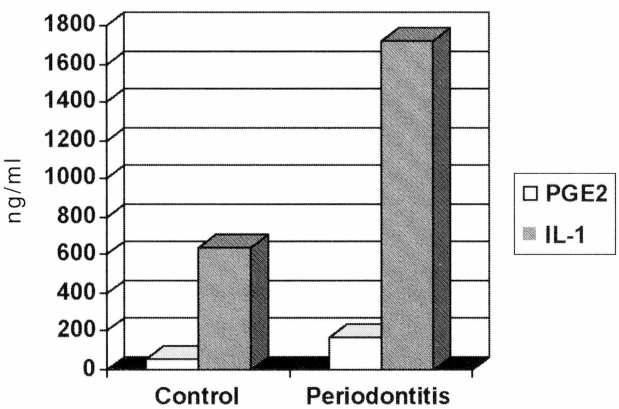

Figure 1. — In the periodontitis group there was a significant elevation of GCF levels of both PGE_2 and IL-1β as compared to the control group (NBW).

have the potential to influence pregnancy [19]. Secondly, the physiological mediators of labour include PGE_2 and IL-1β, both of which have been shown to be locally elevated as part of the host response to the microbial challenge in periodontal disease [20]. Thirdly, despite the considerable progress in describing the risk factors involved in PLBW, a high proportion of PLBW cases have an unexplained etiology. Some researchers, in a case-control study, after controlling for other risk factors, concluded that periodontal disease is a statistically significant risk factor for PLBW [4]. While the data do not preclude the possibility that the association between periodontal disease and PLBW may be the reflection of the patient's altered inflammatory trait, which places the patient at risk of both conditions, evidence that a periodontal pathogen can elicit PLBW was obtained in animal models, where subcutaneous infection with Porphyromonas Gingivalis and experimental periodontal disease in pregnant hamsters resulted in decreased fetal growth as well as increased inflammatory mediator levels [21, 22]. According to these results, we found that periodontal disease, in our patients, in absence of other risk factors, can lead to PLBW. In fact, primiparous mothers delivering PLBW infants had significantly worse periodontal disease than controls and a significant elevation of cytokine in GCF was found. In conclusion, poor periodontal health of pregnant women is a risk factor for PLBW. The importance of these findings lies in the fact that poor periodontal health is a factor that is easily amenable to prevention. Future studies would be helpful in determining whether periodontal therapy can reduce the risk of PLBW.

References

[1] Collins J.G. *et al.*: "Effects of Escherichia coli and Porphiromonas gingivalis lipopolisaccharide on pregnancy outcome in the golden hamster". *Infect. Immun.,* 1994, *62* (10), 4652.

[2] Dasanayake A.P.: "Poor periodontal health of the pregnant women as a risk factor for low birth weight". *Ann. Periodontol.,* 1998, *3* (1), 206.

[3] Davenport E.S., William C.E.C.S., Sterne J.A.C., Sivapathasundram V., Fearne J.M., Curtis M.A.: "The East London Study of maternal chronic periodonalt disease and preterm low birth weight infants: study design and prevalence data". *Ann. Periodontol.,* 1998, *3* (1), 213.

[4] Offenbacher *et al.*: "Periodonatl infection as a possible risk factor for preterm low birth weight". *J. Periodont.,* 1996, *67* (suppl. 10), 1103.

[5] Offenbacher *et al.*: "Potential phatogenetic mechanism of periodontitis-associated pregnancy complications". *Ann. Periodontol.,* 1998, *3* (1), 233.

[6] Di Placido *et al.*: "Lesioni gengivali iperplastiche in gravidanza". Nota II. *Min. Stomatol.*, 1998, *47* (5), 223.

[7] Sconyers J.R., Crawford J.J., Moriarty J.D.: "Relationship of bacteremia to toothbrushing in patient with periodontitis". *J. Am. Dent. Assoc.,* 1973, *87*, 616.

[8] Kinane D.F.: "Periodontal diseases contributions to cardiovascular disease: an overview of potential mechanism". *Ann. Periodontol.,* 1998, *3* (1), 142.

[9] Romero R., Mazor M., Wu Y.K., Avila C., Oyarzun E., Mitchell M.D.: "Bacterial endotoxin and tumor necrosis factor stimulate prostaglandin production by the human decidua". *Prostaglandins Leukot Essent Fatty Acids,* 1998, *37*, 183.

[10] Romero R. *et al.*: "Amniotic fluid prostanoid concentration increase early during the course of spontaneous labor at term". *Am. J. Obstet. Gynecol.*, 1994, *171* (6), 1613.

[11] Romero R. *et al.*: "The relationship between spontaneous rupture of membranes, labor and microbial invasion of the amniotic cavity and amniotic fluid concentration of prostaglandins and thromboxane B in term pregnancy". *Am. J. Obstet. Gynecol.*, 1993, *168,* 1654.

[12] Romero R. *et al.*: "Infection and labor. III. Interleukin-1: A signal for the onset of parturition". *Am. J. Obstet. Gynecol.,* 1989, *160,* 1117.

[13] Romero R., Durum S., Dinarello C.A.: "Interleukin-1 stimulates prostaglandin biosynthesis by human amnion". *Prostaglandins,* 1989, *37*, 13.

[14] Romero R., Wu Y.K., Mazor M., Hobbin J.C., Mitchell M.D.: "Amniotic fluid PGE_2 in preterm labor". *Prostaglandins Leukot Essent Fatty Acids*, 1998, *34*, 141.

[15] Tatamani T., Tsunoda H., Iwasaki H., Kaneko M., Hashimoto T., Onozaki K.: "Existence of both IL-1α and IL-1β in normal amniotic fluid: Unique high molecular weight form of IL-1". *Immunology*, 1988, *65*, 337.

[16] Flynn A., Finke J.H., Hilfiker M.L.: "Placental mononuclear phagocytes as a source of IL-1". *Science,* 1982, *218*, 475.

[17] Opsjon S. *et al.*: "Tumor necrosis factor, IL-1 and IL-6 in normal human pregnancy". *Am. J. Obstet. Gynecol.,* 1993, *166*, 397.

[18] World Health Organization: Oral Health Surveys, Basic Method, 3rd (ed.), Geneva, World Health Organization, 1987, 31.

[19] Hilier S.L.K., Matius J., Krohn M.J., Kivat N., Holmes K.K., Eschenbach D.A.: "A case-control study of chorioamnionic infection and chorioamnionititis in prematurity". *N. Engl. J. Med.,* 1988, *319,* 972.

[20] Lamster I.B., Noval M.J.: "Host mediators in gingival crevicular fluid-implications for the pathogenesis of periodontal disease". *Crit. Rev. Oral. Biol. Med.*, 1992, *3,* 31.

[21] Collins J.G., Windley H.W. III, Arnold R.R., Offenbacher S.: "Experimental periodontitis retard hamster fetal growth" (abstr. 1171). *J. Dent. Res.*, 1995, *74* (Spec. Issue), 158.

Address reprint requests to:
G. CARTA, M.D.
Università di L'Aquila
Facoltà di Medicina e Chirurgia
Dipartimento di Scienze Chirurgiche
Via Vetoio, Pal 11/A
67100 Coppito, L'Aquila (Italy)