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Study of the relation between preterm delivery and periodontitis
The role of prophylactic dental therapy in the prevention of preterm delivery

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PhD thesis

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Scientific publications related to the thesis

I. **T. Novák**, M. Radnai, E. Urbán, I. Gorzó, E. Nagy, A. Pál. Periodontitis and its role in preterm delivery in the southeast region of Hungary. *Magyar Nőorvosok Lapja* 2005; 68; 311-314

II. M. Radnai, I. Gorzó, E. Nagy, E. Urbán, **T. Novák**, A. Pál. A possible association between preterm birth and early periodontitis. Pilot study. *Journal of Clinical Periodontology* 2004; 31;736-741 (**IF: 1.582**)

III. E. Urbán, M. Radnai, **T. Novák**, I. Gorzó, A. Pál , E. Nagy. Distribution of anaerobic bacteria among pregnant periodontitis patients who experience preterm delivery. *Anaerobe* 2006; 12; 52-57 (**IF: 0.494**)

IV. M. Radnai, I. Gorzó, E. Nagy, E. Urbán, J. Eller, **T. Novák**, A. Pál. Caries and periodontal state of pregnant women. Part I. Caries status. *Fogorvosi Szemle* 2005; 98; 53-57

V. M. Radnai, I. Gorzó, E. Nagy, E. Urbán, J. Eller, **T. Novák**, A. Pál. Caries and periodontal state of pregnant women. Part II. Periodontal state. *Fogorvosi Szemle* 2005; 98; 101-102

VI. M. Radnai, I. Gorzó, E. Nagy, E. Urbán, J. Eller, **T. Novák**, A. Pál. Possible association between mother's periodontal status and preterm delivery. *Journal of Clinical Periodontology* 2006; 33; 791-796 (**IF: 2.22**)

VII. M. Radnai, A. Pál, **T. Novák**, E. Urbán, J. Eller, N. Heffter, G. Horváth, I. Gorzó. The possible effect of basic periodontal treatment on the outcome of pregnancy. *Fogorvosi Szemle* 2008; 101; 179-185

VIII. **T. Novák**, M. Radnai, I. Gorzó, E. Urbán, H. Orvos, J. Eller, A. Pál. Prevention of preterm delivery in patients with periodontitis. *Fetal Diagnosis and Therapy*, in press, accepted for publication in 31 July 2008. Manuscript 200801019 (**IF: 0.844**)

IX. M. Radnai, A. Pál, **T. Novák**, E. Urbán, J., Eller, I. Gorzó. Benefits of periodontal treatment in threatening preterm birth. *Journal of Dental Research*, in press, accepted for publication in 24 November 2008. Manuscript URG07-0347RRRR (**IF: 3,475**)

Contents

I. Abbreviations (in alphabetical order)

AF	**Amniotic fluid**
BOP	**Bleeding on probing**
CI	**Confidence interval**
g	**gram**
HNHIF	**Hungarian National Health Insurance Fund**
HPG	**Homogeneous patient group**
IL	**Interleukin**
IUGR	**Intrauterine growth retardation**
LBW	**Low birth weight**
ml	**Mililitre**
mm	**Milimetre**
MPD	**Maternal periodontal disease**
MSI	**Major surgical intervention**
NICU	**Neonatal intensive care unit**
OR	**Odds ratio**
p	**p value**
PB	**Preterm birth**
PD	**Probing depth**
PDT	**Preventive dental treatment**
PGE_2	**Prostaglandin E_2**
pH	**pH value**
RR	**Risk ratio**
SD	**Standard deviation**
TNF-α	**Tumor necrosis factor alpha**
TPD	**Threatened preterm delivery**
WHO	**World Health Organization**

II. Introduction

Prematurity plays a major role in perinatal morbidity and mortality in Hungary. The number of live births per year is around 95,000, of which about 8-9% are preterm births (PBs). Approximately 70% of the cases of perinatal mortality occure among premature newborns. If we add the problems of the somatic/mental postnatal care of the surviving PB cases, prematurity must be highlighted, because it remains a significant public health issue and a leading cause of neonatal death and of long-term neurodevelopmental disturbances (1,2). PB through its complexity, imposes an enormous medical, moral burden on the individual, the family and society. Accordingly, every effort to decrease PB and the levels of perinatal morbidity and mortality is welcome.

By definition PB means that the delivery takes place after the completion of 24 weeks, and before the completion of 37 weeks of pregnancy.

The rate of prematurity in the Department of Obstetrics and Gynaecology at the University of Szeged is around 12-15%, with little deviation. This high rate is probably caused by the role of the Department as a tertiary regional centre which means that the majority of the threatened preterm delivery (TPD) cases in the south-east region of Hungary are referred here on the basis of the concept of *in utero* transportation. The Department is in permanent professional contact with the Neonatal Intensive Care Unit (NICU) at the Department of Pediatrics. A statistical breakdown of the leading obstetrical data from the last 7 years is presented in Table 1.

Table 1. The principal obstetrical data at the Department of Obstetrics and Gynaecology, University of Szeged, in the period 2000-2007

Year	2000	2001	2002	2003	2004	2005	2006	2007
Total number of deliveries	1771	2091	1944	2009	1985	2108	2035	2236
Total number of newborns	1822	2146	1998	2089	2063	2175	2107	2305
Total number of premature newborns	242	289	260	316	328	300	274	278
Rate of prematurity (%)	13.28	13.46	13.01	15.12	15.9	13.79	13	12.06

The higher number of deliveries in 2007 was a consequence of the health care unit integration in Szeged, a process which started in that year.

Based on the recently approved Homogeneous Patient Group (HPG) classification, the following Table presents, for illustration, the financial expenditure paid by the Hungarian National Health Insurance Fund (HNHIF) for a pediatric unit, 3 months after completion of the medical services were delivered.

Table 2. The various hospitalization times and the costs covered by the HNHIF for the different HPG groups in the case of newborns. From 1 June 2007, 1 HPG weight number is equivalent to 146,000 Hungarian forints (HUF)

HPG classification	Birth weight of neonates, grams (g)	Hospitalization duration (days)			HPG weight number	Cost of hospitalization (HUF)
		Minimal	Maximal	Normative		
15M7110	**Under 999**	40	100	70	29.49746	4,306,629
15P7120	**1000-1499 with major surgical intervention (MSI)**	21	80	34	13.01718	1,900,508
15M7130	**1000-1499 without MSI**	20	80	43	11.32928	1,654,074
15P7140	**1500-1999 MSI**	16	70	40	11.20756	1,636,303
15M715Z	**1500-1999 without MSI, with major problem**	15	70	32	8.55427	1,248,923
15M7270	**More than 2499, normal neonatal diagnosis**	2	25	5	0.36569	53390

From these data it may be concluded that while the cost for a term newborn (15M7270 HPG) with a normative duration of hospitalization of 5 day is 53,390 HUF, a preterm newborn with a weight at delivery of <1,000 g (15M7110 HPG) has a financial cost for 70 normative hospitalization days around of 4,306,629 HUF. If we add the costs of the postnatal somatic-mental medical care, calculated for the approximately 8,000 premature newborns per year, the total outflow from the HNHIF is around 10-15 billion HUF/year. Other major financial costs, incurred by the social and familial environment, are essentially inestimable.

Accordingly, the prevention of PB is a very important task for the whole of society. The major causes of a predisposition to PB are the social situation, the maternal age, and different maternal illnesses. It is very important for women to take appropriate care during their pregnancy, so as to decrease the effects of the factors which can predispose to failure of the pregnancy, TPD or PB. Conscious family planning also plays a major role in the prevention of PB: the disclosure of previous preterm deliveries, spontaneous/missed abortions, previous intrauterine manipulations (interruption of pregnancy, interventions for anatomical genital disorders), cervical incompetency, smoking, drug and alcohol consumption, sign of stress and mental sickness, severe maternal illnesses and urogenital infections are important factors for the medical care team as concerns the prevention of PB. In pregnancy, recognition of the signs of premature rupture of the membranes, different types of infections, fetal abnormalities, intrauterine growth retardation (IUGR) signs, anatomical and insertional disturbances of the placenta, intrauterine death of the fetus, pregnancies following assisted reproduction procedures and the artificially induced deliveries involving the wrong calculation of the estimated date of delivery is extremely important, as these are the major factors which can lead to PB, similarly as for the actions of drugs, chemical or physical agents, and different types of radiation (teratogenetic effects, abortion and PB, and backwardness in physical or mental development) (4).

The role of maternal infections in the development of complications in pregnancies is well known. In most cases these infections are of urogenital origin, but in a few cases the starting point can be located elsewhere, far from the target organ, i.e. the pregnant uterus.

The role of oral hygiene in the development of different illnesses was known as long ago as in ancient Egypt, Persia, Assyria, and the Greek and Rome Empires (5).

In recent decades, in connection with the examination of the oral diseases, the theory of the focal infection has been substantiated, and correlations have been established between morbidity and mortality and systemic and dental inflammatory diseases (6).

Since the 1990s, a number of studies have revealed relationships between PB and periodontal diseases, with many publications showing that severe, generalized infection of the periodontium may be a possible risk factor for prematurity. In this respect, the studies lead Offenbacher et al. (7) provide the fundamental information. They first reported an association between maternal periodontal disease (MPD) and the delivery of a preterm infant. In a case-control study of 124 pregnant women, they observed that those who delivered before 37 weeks of gestation or who had an infant that weighed less than 2,500 g had significantly worse grade of periodontitis than the control women. The adjusted odds ratio (OR) for delivery of a preterm, low birth weight (LBW) infant was 7 (i.e. about a 7-fold increased risk) suggesting that periodontitis might be a previously unrecognized and clinically significant risk factor for the delivery of a preterm LBW infant. Extrapolation from these data suggested that 18% of the cases of preterm, LBW infants born annually might be attributable to periodontitis, which may therefore account for a significant proportion of the $5.5 billion annual hospital costs associated with the care of small babies. This study was followed by the publication of considerable information from the other authors, in support of this theory.

The main focus points in these scientific publications relate to the study of the periodontal pocket size, and the grade of bleeding of the gingiva, together with the results of the microbiological investigations, and detailed descriptions of the molecular changes which take place in the oral cavity and can finally cause the starting of the uterine activity, and consequently the induction of TPD or PB.

The continuous flow on scientific publications has confirmed that not only the periodontitis, but also gingivitis plays a leading part in the emergence of the signs of TPD and PB (8).

In view of these concepts, in this thesis I consider periodontitis, as an inflammatory disease of the periodontium, and the effects and the role of this disorder in the prematurity. Other studies have shown that periodontitis can be a risk factor for a series of other illnesses such as arteriosclerosis, ischemic heart disease, respiratory infections or diabetes mellitus (9).

The most common clinical signs of periodontitis are an inflamed gingiva, which can initiate its separation from the teeth by the formation of pocket around them.

The following Figures illustrate a healthy gingiva, and the signs of mild gingivitis and severe, generalized periodontitis.

Figure 1. Healthy gingiva

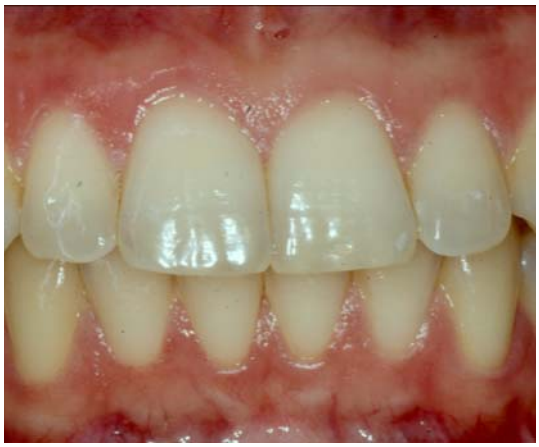


Figure 2. This is a mild gingivitis

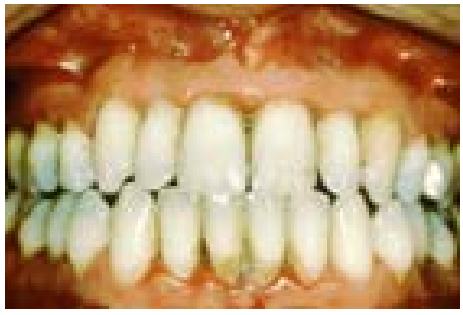


Figure 3. Severe, generalized periodontitis

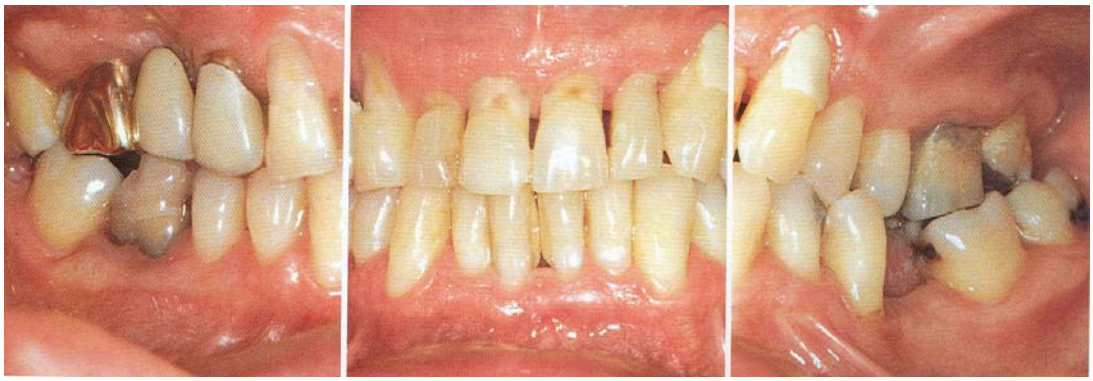
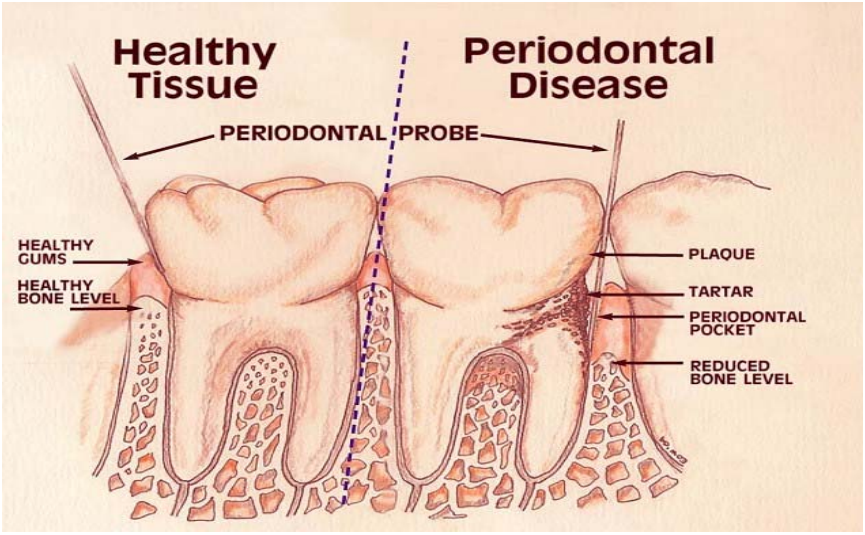


Figure 4 illustrates a healthy tooth and the changes in the periodontium in the event of periodontal disease.

Figure 4. A healthy tooth and the changes accompanying periodontitis.



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It may be seen that, while the gums is intact around the healthy teeth, and the bone level is normal, in the case of periodontitis the most characteristic signs are the appearance of an

inflamed gingiva, plaque, calculus deposits, periodontal pockets and the different grade of the resorption of bone level around the teeth.

It is very important that most studies (including our own) have concluded that oral cavity diseases including periodontitis do not play a primary role in the formation of the factors predisposing to prematurity, but they do play a substantial part in the development of the clinical signs of TPD and PB (10).

Mounting evidence suggests that a chronic oral infection may lead to an immune reaction that either triggers PB or contributes to its onset. The mechanism by which maternal infection mediates early delivery is unclear, but it probably involves both maternal and fetal inflammatory and humoral responses. Genetic variation in the responses to these infections may also play a role in the risk of prematurity. Clinical infections distant from the uterus, including shigellosis and urinary tract infections, have likewise been associated with PB. Infections more proximate to the reproductive tract, such as bacterial vaginosis, trichomoniasis and chlamydial cervicitis, seem to increase the risk for PB. Intrauterine infection and chorioamnionitis also enhance the danger of prematurity.

In the last decade, many investigators were interested in studying the role of subclinical maternal infection in preterm labour. Evidence in support of this theory includes the following:

- increased histologic chorioamnionitis, clinical infection after PB;
- a significant association between some lower genital tract organisms and infections and PB or preterm premature rupture of the membranes;
- positive cultures of amniotic fluid or membranes from some patients with preterm labour and infection markers seen in PB;
- induction of PB in animal models by bacteria or their products;
- the finding in some clinical trials that antibiotics lower the rate of PB or can defer this.

Periodontitis, an oral Gram-negative anaerobic infection, is common in women of childbearing age. It presents as infection and inflammation of the gingiva and supporting structures of the teeth, resulting in destruction of them. Fluid that bathes the teeth at the gingival margin, known as gingival crevicular fluid, often contains inflammatory mediators and the oral pathogens associated with periodontitis.

The mechanisms underlying this destructive process involve both direct tissue damage resulting from plaque bacterial products, and indirect damage through bacterial induction of the host inflammatory and immune responses. Periodontitis affects up to 50% of the population, including a relatively high proportion of pregnant women. Advancing age, smoking and diabetes are some of the risk factors for the development of periodontitis. While periodontitis is a chronic, local oral infection, there is evidence that both local and systemic inflammation may occur.

Despite this limitation, the early studies led to the hypothesis that the bacteria that cause MPD (largely Gram-negative anaerobes) serve as a source of endotoxin and lipopolysaccharides, which increase local inflammatory mediators. It has been theorized that these mediators, including PGE2 and cytokines, may contribute to PB.

In an effort to determine the mechanism of action for a better understanding of the possible mechanism behind the association between periodontitis and PB, researchers have measured gingival crevicular fluid levels of prostaglandin E_2 (PGE_2) and interleukin 1beta (IL-1ß) in mothers who delivered preterm, LBW infants, and compared these levels with those found in control women. They discovered that the gingival crevicular fluid levels of PGE_2 were significantly higher in the case subjects than in the control women. In addition, among primiparous women with preterm, LBW infants, they found significant inverse associations between the birth weight and the gestational age and the gingival crevicular PGE_2, tumor necrosis alpha (TNF-α) and interleukin 6 (IL-6) levels. The maternal and fetal humoral responses to oral pathogens as a possible risk factor or marker for preterm delivery among pregnant women with MPD were also studied. There was a 2.9-fold higher prevalence of neonatal IgM seropositivity for one or more oral pathogens among the preterm neonates, as compared with the term newborns (19.9% vs. 6.9%, respectively, p=0.0015). A lack of maternal IgG antibody to several pathogenic oral organisms was associated with an increased rate of prematurity, (OR 2.2; 95% confidence interval (CI) 1.5–3.8). The highest rate of prematurity (66.7%) was seen in those mothers without any protective IgG response to oral pathogens who delivered a newborn who had an IgM response. These data led the authors to conclude that MPD without a protective maternal antibody response is associated with the systemic dissemination of oral microorganisms that may be passed on to the foetus and result in PB. This in turn led them devise the theoretical scheme outlined in the Table 3.

Table 3. A theoretical mechanism by which periodontitis can lead to PB.

Subgingival plaque and pathogenic microorganisms in the biofilm under the gingival margin
▼
Bacterial products and lipopolysaccharides penetrate the gingiva
▼
The gingiva releases inflammatory mediators
▼
Bacteria, bacterial products and local cytokines invade the systemic circulation
▼
Host inflammatory and humoral responses
▼
Oral bacteria and bacterial products reach the uterus and placenta and/or uterine/placental/foetal inflammatory response
▼
PB

While the correlation between MPD and PB is exciting (and represents a potentially treatable cause of PB), the interpretation of the research findings can be made cautiously. It is possible that MPD may only be a surrogate for other maternal factors that predispose to PB. Furthermore, while the model presented here is biologically plausible, the researchers still have to determine the underlying mechanism by which periodontitis may contribute to PB. Further studies on the maternal and foetal inflammatory responses to chronic oral infection and on the placental pathology in women with MPD are ongoing to determine the relationship between MPD and PB (11).

The aim of this thesis was formulated around this theory. Our studies lead as to conclude that in the south-east region of Hungary recognition of the signs of periodontitis among pregnant women, and the prophylactic treatment of this type of disease may be an important factor in the prevention of TPD and PB, and consequently may lead to improved neonatal indicators relating to the perinatal morbidity and mortality.

III. Aim of the thesis

The aim of the work summarized in this thesis was to answer the following questions:

1. What relation can be found between periodontitis and TPD and PB in the south-east region of Hungary?
2. Is there any modification in the incidence of PB in the event of preventive dental therapy (PDT) undergone by the pregnant observed for TPD?
3. Following PDT what changes are observed in the mean birth weight of the neonate at delivery?
4. What improvement in the OR for term delivery is observed in the event of PDT?
5. Is there any relationship between the newborn status observed at delivery (5-minute APGAR score and the umbilical cord vein pH) and periodontitis in pregnancy?

IV. Material and methods

The study was conducted at the Department of Obstetrics and Gynaecology in Szeged. The participating patients were informed about the aim of the study, and signed the detailed Consent Form for dental, obstetrical and microbiological investigations approved by the Ethics Committee of the University of Szeged. We then performed two studies, according to the following protocols:

1. The first, prospective case-control study, was carried out on a study group (*A*) of 24 patients who gave birth to a premature newborn. The control group (*B*) comprised 45 pregnants who delivered after the completion of 37 weeks of pregnancy, and who did not required treatment for TPD.

The patients participating in the study were volunteers who had delivered in our department. Only systematically healthy patients were enrolled into the study. The criteria for participation were very serious, wich is the reason why the duration of the study was prolonged and the number of enrolled cases was relatively low. We usually made two personal contacts with each patient, at the first time asking them to contribute to this study, while on the next occasion the dental examination was made. The role of these two contacts was to allow the patients to view the interrogator as a known person, so as to facilitate her answers related to her personal background (social situation and education level), and her the maternal attitude concerning the pregnancy (smoking, alcohol or drug use, previous planning of the pregnancy). The obstetrical data were found in the documentation at the time of hospitalization. If the patient was not selected for the study, her personal data were not recorded. The study period was between 1 January 2001 and 31 December 2003. In all cases, when it was necesarry, we contacted the patients' doctors for a detailed information about them.

The selection criteria for the study were:

- willingness to take a part in the study
- singleton, primigravida-primipara pregnancies
- systemically healthy patient without any other disease in her history (e.g. cardiac problems, diabetes, asthma, gastrointestinal or renal diseases)

- non participation in antibiotic treatment for 2 weeks before the examination
- the newborn had no genetical malformation
- the delivery started during hospitalization, and the delivery occurred within 24 hours after admission

The dental examination was performed in three days after delivery, by the dental examiner, at the Department of Obstetrics and Gynaecology, where the subjects were seated in a comfortable chair with a head support, and a dental light source was used. At this time the oral cavity presented the same situation as in pregnancy. An earlier study (12) had demonstrated that gingivitis appears in a healthy patient 21 days after of the suspension of tooth-brushing and 8-9 days the status of gingiva is normalized if the resumption of the oral cavity health measures. This examination followed the WHO guidelines (13): a full periodontal status was taken, which included the plaque index, the presence or absence of calculus, the recession of the buccal marginal gingivae (recorded in mm), tooth mobility recorded on a 0-3 scale, probing depth (PD) (recorded in milimetre (mm)) and bleeding on probing (BOP). BOP was recorded as positive (Yes or No on a scale) if it occurred at any site of the tooth within 15 s after measuring the PD. To measure the PD, a disposable periodontal probe was used with a tip diameter of 0.5 mm. The PD was not recorded at the third molars nor at retained roots. It was measured at 6 sites per tooth i.e. mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingul and distolingual (14). The mode of the measurement of PD is presented in Figure 5.

Figure 5. Measurement of PD

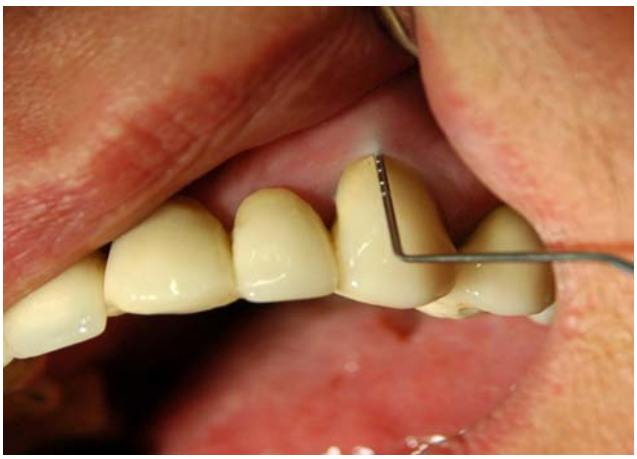

Figure (6) is from custody of I. Gorzó, by his permission.

Criteria for periodontitis: a patient was recorded as having periodontal disease, if she had PD≥4mm (PD4) at at least at one site and BOP for ≥50% of the teeth. Subjects without these criteria were regarded as periodontally healty. The PD4 mm was called the "critical probing depth".

The recorded data included:

- the maternal age at delivery;
- the duration of the pregnancy
- the newborn birth weight at delivery
- the incidence of periodontitis at delivery and the rate of dysmaturity

2. The second study was a comparative prospective examination of two groups of pregnants with TPD, also carried out at the Department of Obstetrics and Gynaecology: Group *C*, (*n*=39) comprised patients who were merely examined dentally for periodontitis, and group *D* (*n*=44), which comprised patients who additionally received PDT. These methods involved supra- and subgingival scaling and polishing, using ultrasonic and manual instruments, plus instruction and motivation for better dental care. The study period was between 1 January 2006 and 31 December 2007. In both groups the delivery could occur either before or after the 37 weeks of pregnancy.

The recorded data included:

- the maternal age at delivery;
- the incidence of periodontitis;
- the duration of pregnancy at delivery;
- the mean birth weight of the newborn
- the role of PDT and what kind changes in the OR for term delivery were observed in these cases;
- the mode of delivery;
- the 5-minutes APGAR score and the umbilical vein pH at delivery.

The inclusion criteria for this study were:

- willigness to take part in the study;
- treatment for TPD during pregnancy;
- singleton, primigravida-primipara pregnancies;
- systemically healthy patient without any other disease in her history

We defined the diagnosis of TPD according to the following criteria:

- gestational age between 24 and 37 weeks;
- documented regular uterine activity and/or
- documented cervical dilation;
- preterm rupture of the membranes.

After hospitalisaton if necessary, the pregnant received special obstetrical measures and therapy, to maintain the pregnancy as long as possible:

- in the first instance, correct estimation of the delivery time, based on the last menstrual period and rigorous physical and ultrasound examinations (duration of the pregnancy, estimated foetal weight, possible eventually genetic/chromosomal abnormalities and cervical score at hospitalisation).
- blood, urine, and vaginal discharge examinations
- depending on the results of the cardiotocographic examination, if necessary the intravenous or oral tocolytic therapy was started, if there was no contraindication;
- the prevention of foetal respiratory distress syndrome, by administration to the patient of 10 mg dexamethasonum natrium phosphoricum (1 ml, 5 mg/vial) 10 mg (Oradexon) by intramuscular injection;
- administration of antibiotics in the event of preterm rupture of the membrane in every case *ex juvantibus*, and in the possesion of the vaginal smear microbiological results, based on the antibiogram.

The most important criteria concerning the start of tocolysis were the regular documentable uterine activity, and/or the cervical score progression or the preterm rupture of the membranes.

For parenteral tocolytic treatment beta-sympathomimetic agents were used: 25 mcg of hexoprenalinium sulfate (5 ml vial Gynipral) administered with Infuzomat 3 ml/hour, or magnesium sulphate (4 or 8 gram/vial) in 500 ml of Ringer-lactat solution, in drop infusion (15 drops/minute).

If the intravenous tocolytic treatment exerted its effect in a suitable manner, the pateint received oral tocolytic therapy continuosly:

- after the Gynipral tocolysis, Spiropent daily 2x1 tabl. (1 tablet of this agent contains 0,020 mg of klenbuterol-hydrochloryd), Seduxen daily 2x1 tabl. (diazepam 5 mg/tablet), Verapamil daily 2x40 mg (80.0 mg of verapamil-hydrochloryd film tablet);
- after the $MgSO_4$ tocolysis, magnesium citrate daily 2x1 tablet (magnesium citricii 500 mg tablet), and Seduxen 2x1 tablet daily.

The contraindications for the tocolytic therapy were:

- a cervical score $\geq$ 5 cm
- acute or chronic intrauterine fetal distress signs (modification of the foetal heart frequency, amniotic fluid with meconium);
- signs of intrauterine infection (maternal fever, leucocytosis, and elevated C-reactive proteine value)
- bleeding from the vagina, and abruption of the placenta

The tocolytic therapy was interrupted at the completion of 36 weeks of pregnancy.

With a view to the homogeneity of the groups, only primigravida-primiparous, singleton, healthy pregnancies were selected for this study. The patients were non-smokers, and were selected so that the role of additional risk factors for PB such as a socio-economic status, or a poor nutritional status, was non-significant. For this reason, the overall number of patients was relatively low, but only those who met the severe criteria for selection were enrolled. Generally it should be mentioned that from the pregnants displayed true interest, and a positive attitude to the examinations and findings.

Before the study, a sample size calculation was performed which related the birth weight assessment and the duration of gestation. For a two-sample *t*-test with 90% test power and 0.05 error rate, assuming a 500 g birth weight difference at 650 g standard deviation (SD), n=37 was the necessary case number, and to prove a 1.5 week difference in delivery time, at 2 weeks SD, the desired minimum sample size was n=39.

The patient selection for the two groups was randomized, by the dental examiner, based on the throw of even or odd numbers with a dice. The patients were familiarized with the form of consent before the randomization procedure was performed. Only the patients who met the severe criteria for the study were enrolled.

In the case of an odd number on the dice, only the dental examination and the status assesment were performed, while additional PDT was carried out in the case of the throw of an even number. For odd numbers patients the PDT was offered after the delivery if the pregnant wished to have it. The PDT essentially comprised mouth hygiene instruction (the usage of a toothbrush and tooth-brushing techniques, and the usage of the dental floss) and supra- and subgingival scaling and polishing, using ultrasound and manual instruments.

Statistical analysis: To compare continuous data between the two groups, we first checked the normal distribution of the data by using the Kolgomorov-Smirnov test. As the data were found to be not normal, we used the Mann-Whitney test for the comparisons. For categorical data, the chi-squared test and Fisher's exact test were used.

V. Results

1. In the first study, we enrolled 24 patients in the case group (*A*, preterm delivery) and 45 in the control group (*B*, delivery at term).

The average maternal age at delivery was the same in the two groups. The difference in duration of pregnancy at delivery was a consequence of the enrollment criteria. The mean newborn weight at delivery was considerable lower in the case group, than in control group. In the case of PB, the mean duration of pregnancy at delivery was likewise lower than in the control group. The concomitant presence of periodontitis and a low birth weight was observed in 3 cases in the case group. Because of the low number of cases, we did not make any calculation of the significance level. These data are presented in Table 4.

Table 4. Data relating to maternal age, birth weight of neonate and mean duration of pregnancy

	Case group *A* (*n*=24)	**Control group *B* (*n*=45)**
Mean maternal age (year)	28	28
Mean birth weight (g)	2384	3494
Mean duration of pregnancy (weeks)	34.9 (32-36)	39.7 (37-41)
Periodontitis and low birth weight	3	0

The frequency of periodontitis in the two groups is presented in Table 5. In the case group, the existence of at least one site with PD≥4 cm and BOP diplayed the strongest significance with regard to an adverse pregnancy outcome, as compared with the control group.

Table 5. The incidence of PD4, and BOP in the groups, individually and paired, in conformity with the definition of periodontitis.

	Case group ***A*** **(*n*=24, 100%)**	**Control group** ***B*** **(*n*=45, 100%)**	***p* value**
PD4			
Yes	**13 (54.1%)**	**17 (37.7%)**	
No	**11 (45.9 %)**	**28 (62.3%)**	
BOP			
Yes	**13 (54.1%)**	**12 (26.6%)**	
No	**11 (45.9%)**	**33 (73.4%)**	
Periodontitis (PD4+BOP)			
Yes	**12 (50%)**	**8 (17.7%)**	**0.004**
No	**12 (50%)**	**37 (82.3%)**	

PD4 around the teeth was appreciably more frequent in the case group, than in the control. BOP was found in the same percentage in the case group, but only half as often in the control group.

When the interactions between the signs of periodontitis were considered pairwise, BOP and the existence of at least one site with PD4 exhibited the strongest significance with an adverse pregnancy outcome (p=0.004). Half of the women in the case group had periodontitis, in comparison with less than one-fifth in the control group.

These results permit the conclusion that in the south-east region of Hungary periodontitis may be a risk factor for TPD and PB (16).

2. In the second study, on the basis of the inclusion criteria, 39 patients were enrolled in case group *C* (only dental examination) and 44 patients in the control group *D* (dental examination and PDT). The dental examination, and establishment of the dental status in this study were performed after the period of hospitalisation, and in group D the PDT was

performed at the same time in all of the cases, independently, of wether the patient had or not periodontitis, based on the criteria as mentioned before.

The incidence of periodontitis was rather similar in the two groups: (p=0.513). These data are presented in Table 6.

6. Table. The incidence of periodontitis in the two groups

Group	Incidence of periodontitis	Fisher's exact test
***C* without PDT (*n*=39, 100%)**	**48.7% (*n*=19)**	**p=0.513**
***D* with PDT (*n*=44, 100%)**	**40.9% (*n*=18)**	

We did not detect a significant difference in the average maternal age between the two groups: 27.7 and 27.3 years respectively.

As regards the mode of delivery, in group C this was *per vias naturales* in 28 cases, and by caesarian section in 11 cases. In this group periodontitis was found in 5 cases in the vaginal delivery subgroup, and also in 5 cases in the caesarian section subgroup.

In the periodontally treated group, 26 vaginal deliveries and 18 caesarian sections were recorded. In the latter subgroup, in the same mode, there were 5 patients with manifest periodontitis.

Since the mode of delivery depends in a very dynamic manner on the momentary situation (e.g. the acute or chronic intrauterine distress, the dilation of the cervix, the presentation of the foetus, and the uterine activity), we consider that the effect of this as concerns principal aim of this thesis can not be examined. It follows from this that the 5 minute APGAR values and the umbilical cord venous sample pH values measured at the time of birth did not show a significant difference between the two groups. Accordingly, a direct connection cannot be deduced between the objective judgement of the periodontitis during the the pregnancy and the newborn status detected at the moment of delivery. The statistical calculations were made with the Mann-Whitney test.

The data are presented in the Table 7.

Table 7. 5-minute APGAR values and the umbilical cord vein pH observed at the time of delivery

Group	5-minute APGAR value		Umbilical cord vein pH	
	Average	SD	Average	SD
C (*n*=39)	9.44	±1.071	7.233	±0.1057
D (*n*=44)	9.68	±0.909	7.268	±0.0831
p value	0.127		0.083	

At delivery, the mean gestational age in group C was significantly shorter than in group D (p=0.011). Likewise there was a significantly (*p*=0.007) lower newborn birth weight in group C, than in group D, justifying the hypothesis that the PDT during pregnancy has a favourable effect in the prolonging gestation and hence in the achievement of a higher birth weight. These data are presented in Table 8. The statistical calculations were performed with the Mann-Whitney U test.

Table 8. The mean duration of pregnancy and the newborn birth weight in groups C and D

Group	Gestational age at delivery		Newborn weight at delivery	
	Mean	SD	Mean	SD
C (*n*=39)	36.08	±2.757	2580.8	±668.5
D (*n*=44)	37.52	±1.923	3009.1	±711.3
p value	0.011		0.007	

The possibility of the prolongation of the pregnancy, in the case of TPD, and the prospect of being able to reach the full term of foetal maturity can improve the status of the newborn, and consequently lead to better parameters regarding neonatal morbidity and mortality.

Statistically similar numbers of newborns were transferred to the NICU: 10 from the deliveries in group *C*, and 10 from the deliveries in group *D*. As concerns these transfers, periodontitis was demonstrated in 6 cases in group *C*, and in 2 cases in group *D*. The low number of cases did not allow determination of a level of significance. Perinatal mortality was not observed among the studied cases.

The statistical analysis revealed a significant difference between the two groups as regards the rate PB, which was twice as high in group *C*, as in group *D*. From these results, we concluded that PDT in pregnancy has a salutary effect in prolonging the length of pregnancy (p=0.012).

In the case of TPD, the periodontal treatment of the pregnant, can increase the chance of term delivery and reduce the chance of PB to 0.286 (95% CI:0.113-0.723). The data calculated with the Fisher exact test are presented in Table 9 (17).

Table 9. The increase in the OR for term delivery in the event of PDT

Group	The rate of preterm delivery	p=0.012
***C* (*n*=39)**	**53.8% (n=21)**	**OR=3.5 (CI:1.38-8.86)**
***D* (*n*=44)**	**25% (n=11)**	

It is probable, that the risk of PB is higher if the signs of periodontitis with the criteria applied in this study are more expressed.

VI. Discussion

The care of the complicated pregnancies, and with in this the TPD occupies an important position in the daily task of the medical team responsible for this. The responsibility is enormous, because the consequences of this obstetrical pathology, can influence not only the individual, but also the hole of the family involved, and hence society in general.

On the other hand, the development of the symptoms of the illness in many cases, is independent of the medical profession, and cannot be influenced by the medical team (e.g. the social situation). It is very important to take advantage of all of the available means that can prevent the development of potential complications in pregnancy. In this sense the role of the prophylaxis receives new highlight.

Besides the reduction of the risk factors (e.g. the elimination of negative workplace circumstances (stress and toxic effects), the ordering of bed rest, the recommendation of a suitable lying position, the insurance of an abundant liquid intake, the prohibition of sexual contact, and appreciate psychical support), the clinical symptoms of TPD, may in many cases necessitate clinical hospitalization of the pregnant. In this situation, the previous proposals may be complemented with medical treatment if this is needed. This means parenteral or oral tocolytic treament, and the prevention of the foetal respiratory distress syndrome through the administration of steroids for the foetal lung maturation, combined with antibiotic therapy. In the case of cervical dilation cerclage operation can be performed, if it is considered necessary (18).

Taking all of the relevant factors into consideration, the rate of PB in Hungary can not be reduced to a significant degree.

The results of epidemiological research from the past 10 years support the hypothesis that chronic oral cavity infection, including periodontitis, can be important risk factors in the development of preeclampsia, PB and intrauterine growth retardation (IUGR), which can lead to poorer foetal morbidity and mortality. Periodontitis in women of fertile age (which affects approximately half of them) is a results of the invasion into the oral cavity the anaerobic Gram-negative bacteria. It can cause the loss of the attachment of the teeth, the inflammation of the gums, and the formation of calculus deposits and periodontal pockets. The anaerobic

bacteria and their products can be found in a thin pellicle around the teeth, this containing endotoxins and lipopolysaccharides, too. These materials can increase the secretion of local inflammatory mediators (usually PGE_2 and cytokines), which can lead finally to the development of the clinical signs of TPD and PB. The exact mechanism, by which these inflammatory agents can induce the uterine activity, is not known, but it is supposed that they are playing very important part in the appearance of contractions, and consequently cervical dilation, and in eventually preterm rupture of the membranes. If the number of periodontal pockets around the teeth in enhanced the process of the loss of the attachment increases, and the surface through which the inflammatory mediators can reach the capillary vessels is higher too. For example a 4-5 mm periodontal pocket is an open wound surface around the teeth. The mediators manage to pass into the systemic circulation and through the inflammatory and humoral interactions initiate the response from the target organ, in this case, usually the uterus. If the periodontitis is generalized, this surface can increase too. In this case, the usual oral health measures are not sufficient to stop this process. The bone resorption, the formation of new pockets, and the continuous bacterial infection finally give rise to a vicious surface in which prevention can play an important role.

The recent results of epidemiological and clinical research led us, in the first part of our study, to examine in the south-east region of Hungary, whether the periodontitis that occurs in pregnancy, can be connected with PB. The examinations justified such a connection.

The main obstetrical indicators at our department indicate that while the number of deliveries is rising slightly, the number of PB is relatively stagnant. In the cases of TPD, we investigated the effect of the applied PDT on the length of the pregnancy, and consequently on the neonates birth weight. Our study demonstrated that PDT during pregnancy can increase the chance of term delivery at time with 3.5, and reduce the chance of PB to a factor of 0.286.

Xiong et al. (19) made a meta-analysis of 44 studies accessed by the internet (26 case-control, 13 cohort, and 5 controlled trials). The studies focused on preterm LBW, PB, birth weight by gestational age, miscarriage or pregnancy loss, preeclampsia, and gestational diabetes mellitus. Of the chosen studies, 29 suggested an association between periodontal disease and an increased risk of adverse pregnancy outcome ((ORs) ranging from 1.10 to 20.0) and 15 found no evidence of an association (ORs ranging from 0.78 to 2.54). A meta-analysis of the clinical trials suggested that oral prophylaxis and periodontal treatment may

reduce the rate of preterm LBW (pooled risk ratio (RR): 0.53, 95% [CI]: 0.30-0.95, p<0.05), but did not significantly reduce the rates of PB (pooled RR: 0.79, 95% CI: 0.55-1.11, p>0.05) or LBW (pooled RR: 0.86, 95% CI: 0.58%1.29, P>0.05). The authors concluded that periodontal disease might be associated with increased risk of adverse pregnancy outcomes.

Manau (20) deduced that the significance of the association between periodontal disease and pregnancy outcomes may be determined by the definition of periodontal disease or the measurement procedures used.

In the study conducted by Tarranum et al (21) all of the participating women underwent a full-mouth periodontal examination, including oral hygiene index-simplified, bleeding index and clinical attachment level. The women in the treatment group received non-surgical periodontal therapy during the gestational period, while those in the control group received periodontal treatment after delivery. The periodontal therapy included plaque control instructions and scaling and root planing performed under local anaesthesia. The outcome measures assessed were the gestational age and the birth weight of the newborn. From their results, they concluded that the non-surgical periodontal therapy can reduce the risk of PB in mothers who are affected by periodontitis.

The study by Alvez (22) included 59 women seen at two maternity hospitals. Nineteen mothers had premature and low birth weight babies (gestational age <37 weeks and birth weight <2.500, group I), and 40 had mature, normal weight babies (gestational age >37 weeks and birth weight >2,500 g, group II). Their findings led them to conclude a higher rate of periodontal disease in group I (84.21% - 16/19) as compared with group II (37.5% - 15/40). The data also showed a significant association between periodontal disease and preterm LBW (OR = 8.9 - 95% CI: 2.22-35.65, p = 0.001). In their opinion the MPD was an associated factor for PB and LBW.

In a study conducted in our own department (23), related to intrauterine growth retardation Mészáros et al. found a significant correlation between the maternal body mass index, smoking during pregnancy, the educational level, the social situation, the type of working and the dysmaturity. Many of the cases of dysmaturity and the elimination of the adverse circumstances observed were only partly medical tasks.

Siqueira et al. (24) suggested that periodontitis is associated with systemic features alterations such as an adverse pregnancy outcomes. Their case-control study was conducted to

determine the association between maternal periodontitis and PB, LBW, and IUGR. After adjustment for variables of interest they concluded, that maternal periodontitis is associated with an increased risk of the pathological obstetrical situation, mentioned above.

Gibbs (25) emphasized that in the era of tocolytic therapy, the frequency of PB is not decreasing in a significant manner. PB with its subsequent morbidity and mortality is the leading perinatal problem in the United States, too. Infants born before 37 week of gestation account for approximately 6% to 9% of all births, but for 70% of all perinatal deaths and half of all cases of long-term neurologic morbidity. Current approaches focus on symptomatic treatment. Evidence from many sources links PB to symptomatic infections and some antibiotic trials have shown a lower rate prematurity or have deferred preterm birth.

Hill (26) have found a correlation between PB and the presence Fusobacterium nucleatum, a species, the oral opportunistic pathogen most frequently isolated from AF cultures among women with PB and intact membranes.

In a case-control study carried out to examine the distribution of anaerobes in pregnant women with periodontitis who experienced PB, Urbán et al (27) detected anaerobic bacteria in higher numbers in all of the subgingival plaque samples from the patients when there was clinical evidence of early localized periodontitis. In the periodontitis cases the number of species was 8-14, and the mean newborn birth weight was 2980 g, whereas in cases without periodontitis the number of isolated anaerobic species/patient was 0-4, and the mean newborn birth weight was 3200 g. They provided microbial evidence that MPD and the presence of key pathogens are significant contributors to the obstetric risk of preterm delivery.

In an investigation of the association between cytokines in the AF and PB, the isolation of bacteria from the AF or chorioamnion, and histologic chorioamnionitis Hiller et al (28), were performed the amniocentesis in a 50 afebrile women with intact membranes in preterm labour at or before 34 weeks gestation. Cytokine levels were measured in the AF, and cultures were performed. Placentas were cultured and examined histologically. They found that 32 (64%) of the 50 patients delivered at or before 34 weeks of gestation. Delivery at or before 34 weeks, compared with delivery after 34 weeks, was related to increased levels of IL-6 (88 versus 12%; $p < 0.001$), IL-1 alpha (50 versus 6%; $p=0.004$), IL-1 beta (42 versus 0%; $p= 0.002$), and PGE2 (66 versus 22%; $p =0.008$). Bacteria were recovered from the AF of nine (18%) of the 50 patients. All of the cytokines with increased levels, plus TNF-alpha,

were related to bacteria in the AF. Increased levels of IL-6, IL-1 alpha, IL-1 beta, TNF-alpha, and PGE2 were also associated with histologic chorioamnionitis among women who delivered within 1 week of amniocentesis. Elevated cytokine levels were not related to chorioamnion infection. They concluded that the elevated AF cytokines and PGE2 predicted delivery before 34 weeks of gestation and delivery within 7 days of the amniocentesis, and also AF infection and histologic chorioamnionitis. These findings support the hypothesis that infection is one cause of PB, operating via a mechanism involving the induction of cytokine production.

Jeffcoat et al. (29) conducted a prospective study to test whether chronic periodontal infection is associated with PB. A total of 1,313 pregnant women were recruited from the Perinatal Emphasis Research Center at the University of Alabama at Birmingham. Complete periodontal, medical and behavioral assessments were made between 21 and 24 weeks of gestation. After delivery, medical records were consulted to determine each infant's gestational age at birth. From these data, the authors calculated relationships between MPD and PB, with adjustments for smoking, parity (the state or fact of having born offspring), race and maternal age. They concluded that the patients with severe or generalized periodontal disease had adjusted ORs (95 percent CI) of 4.45 (2.16-9.18) PB (i.e. before 37 weeks of gestational age). The adjusted OR increased with increasing prematurity to 5.28 (2.05-13.60) before a gestational age of 35 weeks and to 7.07 (1.70-27.4) before 32 weeks. Pending an answer as to whether periodontal treatment can decrease the rate of prematurity, it remained appropriate to advise expectant mothers about the importance of good oral health.

Some of the literature references e.g. McGaw (30), referring to the classification of suitable patient material, note that prospective interventional studies are necessary before periodontitis can be regarded as a causal factor for prematurity and PB. Holbrock et al (31) did not detect PB in 96 pregnant women who had PD4, and they found no correlation between MPD and PB. Similarly, Mitchell-Lewis et al. (32) did not observe any significant correlation between the clinical periodontal status in PLBW cases and women with a normal birth outcome.

It is clear, that the literature data are not uniform regarding the inferences drawn concerning a relationship between periodontitis and PB. This can probably be attributed in part to the different criteria for the enrolment of the patients into the studies.

In our own studies we did not analyse a high number of cases, because of the severe criteria for inclusion into the examination (only primigravida-primipara, singleton pregnancies, with negative history were admitted). We made an effort to compile two groups that were comparable from a statistical viewpoint. This is the reason why the study period was relatively long.

Setting out from the assumption verifying the hypothesis of the first study, we found a clear connection between periodontits and PB in the patients from the south-east part of Hungary. On the basis of our results, for the first time in Hungary a dental examination room was established at Department of Obstetrics and Gynaecology in Szeged, where we can carry out examinations and provide prophylactic periodontal treatment for the pregnant women. The data obtained have demonstrated a significant decrease of the incidence of the PB following the PDT, among women observed for TPD. The mean newborn birth weight in the cases who received PDT was significantly higher than in the cases where only the dental status examination was performed. We additionally concluded, that in the case of TPD, dental treatment of the pregnant women can increase the chance of the delivery at term by 3.5, and can reduce the chance of PB to 0.286 (95% CI:0.113-0.723). We did not detect any correlation between the newborn status at delivery (based on 5-minutes APGAR score and umbilical vein pH after delivery) and the presence or not of maternal periodontitis during pregnancy.

From our results, we concluded, that pregnant women should be taught about the correct oral hygiene measures, and if necessary should undergo professional removal of the plaque and calculus from the teeth by depuration, thereby reducing the mediators of inflammation which can lead to preterm uterine activity and consequently induce PB.

We strongly recommend that dental check during pregnancy and treatment should take its worthy place within the framework of the prenatal care. It is necessary draw to the attention of all of the specialist involved (district nurses, obstetrician gynaecologists, family doctors, dentists) and the media to the fact that it is essentially a safe, simple and cheap method whereby serious individual, family, social and society problems can be significantly reduced.

It is very important to stress that additional multicentre, randomized, controlled clinical trials are required to confirm and interpret the causal connection between periodontitis and PB.

VII. Scientific presentations related to the thesis

1. A. Pál, T. **Novák**, E. Urbán, M. Radnai, E. Dósa, I. Gorzó, E. Nagy: The possible role of periodontitis in the ethiology of threatening prematur labor, XVIII International Congress „The Fetus as a Patient", Budapest, 2002.04.25-28, Fetal Diagnosis and Therapy 17; S1 02: 90 (**IF: 0,879**, abstract)
2. Radnai M**.**, Gorzó I., Eller J., Urbán E., Nagy E., **Novák T.**, Pál A.: Periodontitis, mint a koraszülés egyik lehetséges rizikótényezője. No. 33. Magyar Fogorvosok Egyesülete (MFE) Árkövy Vándorgyűlése, a Fogorvos Világszövetség 2002. évi bécsi kongresszusának társkonferenciája, Bécs 2002. október 1-5.
3. **Novák T**., Radnai M**,** Urbán E., Nagy E., Eller J., Gorzó I., Fazekas A., Pál A.: A periodontis szerepe a koraszülésben, alacsony születési súly kialakulásában és a fenyegető koraszülés patomechanizmusában. (Poszter 7), Szülészeti és Perinatológiai Aneszteziológiai Társaság IX. Kongresszusa, Pécs, 2003. március 28.
4. I. Gorzó, M. Radnai**,** E. Urbán, E. Nagy, **T. Novák**, A. Pál: Low birthweight and chronic gingivitis. Europerio 4, Berlin, Germany 19-21 June 2003, Journal of Clinical Periodontology, 30; Suppl. 4, No 133, 2003 (**IF: 1.582**, abstract)
5. I. Gorzó, M. Radnai, U. Urbán, E. Nagy, **T. Novák**, A. Pál: A possible association between pre-term low birth weight and chronic gingivitis and/or early periodontitis. Pilot Study. 81st General Session of the IADR, 2nd Meeting of the PEF (British, Continental European, Irish, and Scandinavian Divisions of the IADR), Göteborg, Sweden June 25-28, 2003, J Dent Res, 82; Spec. Iss. B (Göteborg Abstracts) June No 1158, 2003 (IF: **2.702** abstract*)*
6. Radnai M**.,** Gorzó I., Fazekas A., Pál A., **Novák T**., Eller J.: Terhes nők parodontális és fogazati állapotának felmérése. Assessment of periodontal condition and dental state of pregnant women. P B9 pp. 40. A Magyar Fogpótlástani Társaság XV., a Magyar Fogorvosok Implantológiai Társasága V. és a Magyar Parodontológiai Társaság XIII. Kongresszusa, Budapest, 2003. augusztus 28-30.
7. **Novák T**., Radnai M**.**, Urbán E., Gorzó István, Nagy E., Pál A.: A fenyegető koraszülés és a periodontitis közötti összefüggések tanulmányozása. (P), Magyar Perinatológiai Társaság II. Kongresszusa, Balatonfüred, 2003. szeptember 12-13.

8. **Novák T.**, Radnai M., Urbán E., Nagy E., Eller J., Gorzó I., Fazekas A., Pál A.: A periodontitis szerepe a koraszülésben, alacsony születési súly kialakulásában és a fenyegető koraszülés patomechanizmusában, Magyar Nőorvos Társaság Délmagyarországi Szekciójának XIV. Tudományos Ülése, Gyula, 2003. október 3-4.
9. Radnai M., Gorzó I., Urbán E., Nagy E., **Novák T.**, Pál A., Eller J.:Terhes nők kariológiai állapotának felmérése Délkelet-Magyarországon. Abstr. 31., Tudományos Továbbképző Konferencia és Fogorvostalálkozó, Szeged, 2004. április 23-24.
10. **T. Novák**, M. Radnai**, E.** Urbán, I. Gorzó, E. Nagy, A. Pál: Periodontitis and its role in preterm delivery and low birth weight. Poster 33, pp. 106., The 18th European Congress of Obstetrics and Gynaecology, Athens, Greece, May 12-15, 2004
11. E. Urbán, E. Nagy, M. Radnai**, I.** Gorzó, **T. Novák**, A. Pál.: Microbial investigation of the possible association between pre-term birth and early periodontitis. 14th European Congress of Clinical Microbiology and Infectious Diseases. Praque, 2004, Clinical Microbiological Infection 10, Suppl. 3., 547, 2004. (IF: **2.361** abstract)
12. I. Gorzó., M. Radnai., J. Eller, T. **Novák**, A. Pál, E. Urbán, E. Nagy: Dental care and preterm birth. 4th Preventive Dental Conference Strategies in Oral Health Promotion and Prevention for Europe (Cosponsored by the World Health Organization, Regional Office for Europe), November 14-15, 2003 Budapest, Hungary, Fogorvosi Szemle 97; (1) 50, 2004.
13. Radnai M.**,** Gorzó I., Nagy E., Urbán E., Eller J., **Novák T**., Pál A.: Terhes nők parodontológiai állapotának felmérése Délkelet-Magyarországon. Abstr. 33., Tudományos Továbbképző Konferencia és Fogorvostalálkozó, Szeged, 2005. április 22-24.
14. **Novák T**., Radnai M, Urbán E., Gorzó I., Nagy E., Pál A., A koraszülés prevenciója intézetünkben elvégzett fogászati kezeléssel, A MNT Dél- Magyarországi szekciójának XXVI. Tudományos Ülése, Békéscsaba, 2005.09.30-10.01.
15. Radnai M., Gorzó I., Nagy E., Urbán E., Eller J., **Novák T**., Pál A.: A korai lokalizált parodontitis és a koraszülés lehetséges összefüggése. Early localised periodontitis; a possible risk factor for preterm birth. MFE fogpótlástani Társasága XVI., Magyar Fogorvosok Implantológiai Társasága VI., Magyar Parodontológiai Társaság XIV. Kongressusa, Sopron, 2005, október 13-15.

16. **Novák T**., Radnai M., Urbán E., Gorzó I., Orvos H., Pál A., : A koraszülés megelőzése a délmagyarországi régióban a periodontitisben szenvedő terhesek körében elvégzett preventív fogászati kezeléssel. A MNT Dél- Magyarországi szekciójának XXVI. Tudományos Ülése, Makó, 2005.10.13-14.
17. M. Radnai, I. Gorzó, E. Nagy, E. Urbán, **T. Novák**, A. Pál. A possible association between preterm birth and early periodontitis. Pilot study (Editorial comment). *Obstetrics and Gynecology Survey* 2005; 60; 150-151 (**IF: 2.000**)

VIII. Bibliography

1. Egészségügyi közlöny: 2006; 17; 2495-96
2. Papp Z. (szerk.): A szülészet-nőgyógyászat tankönyve, Semmelweis Kiadó, Budapest, 1999; 413-418
3. Egészségügyi Közlöny: 2007; LVII évf. 13; 1708
4. Doszpod J. (szerk.): Az intrauterin magzat, Medicina, Budapest; 2000; 373
5. O'Reilly PG., Claffey WM.: A history of oral sepsis as a cause of disease. Periodontology 2000; 23; 13-18
6. Slots J.: Update on general health risk of periodontal disease. Int Dental J 2003; 53; 200-207
7. Offenbacher S. et al.: Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996; 67; 1103-1113.
8. Lopez NJ., Da Silva I., Ipinza J., Gutiérrez J.: Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. J Periodontol 2005; 76 (11Suppl); 2144-53
9. Zeeman GG., Veth EO., Dennison DK.: Focus on primary care: periodontal disease: implications for women's health. Obstet Gynecol Surv 2001;56; 43-9
10. Lindhe J.: Examination of patients with periodontal disease: Clinical Periodontology and Implant Dentistry, 4th edition, Blackwell, Munksgaard 2003; 409, ISBN 9781405102360
11. Bogges KA.: Is there a link between periodontal disease and preterm birth?. Contemporary Ob/Gyn 2003; 48; 79-84
12. Löe H., Theidale E., Jensen SB., Shiött CR.: Experimental gingivitis in man III. J. Period Research 1967; 2; 282-289
13. Oral Health Surveys Basic Methods: 3rd edition, WHO, Geneva; 1987; 19-21, ISBN 90-9021-760-1

14. Radnai M., Gorzó I., Nagy E., Urbán E., Eller J., Novák T., Pál A.: A terhes nők kariológiai és parodontológiai állapotának felmérése II. A parodontális állapot. Fogorvosi Szemle 2005; 98; 101-102
15. Papp Z. (szerk.): Szülészet-Nőgyógyászati protokoll, Golden Book Kiadó, II. Kiadás, Budapest 2002; 412
16. Novák T., Radnai M., Urbán E., Gorzó I., Nagy E., Pál A.: A koraszülés és a periodontitis közötti összefüggések tanulmányozása a dél-magyarországi régióban. Magyar Nőorvosok Lapja 2005; 68: 311-314
17. T. Novák, M. Radnai, I. Gorzó, E. Urbán, H. Orvos, J. Eller, A. Pál.: Prevention of preterm delivery in patients with periodontitis. Fetal Diagnosis and Therapy, in press
18. Kornya L. (szerk.): Betegség enciklopédia, Springer, 2. kötet, Budapest, 2002; 1048
19. Xiong X., Buekens P., Vastardis S., Yu SM.: Periodontal disease and pregnancy outcomes: state-of-the-science. Obstet Gynecol Surv 2007 Sep; 62(9); 605-15.
20. 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 May; 35(5), 385-97
21. Tarannum F., Faizuddin M.: Effect of periodontal therapy on pregnancy outcome in women affected by periodontitis. J Periodontol 2007 Nov; 78; 2095-103
22. Alves RT., Ribeiro RA.: Relationship between maternal periodontal disease and birth of preterm low weight babies. Braz Oral Res 2006 Oct-Dec; 20(4); 318-23
23. Mészáros Gy., Novák T., Rigó A., Nyári T., Pál A.: Az intrauterine retardáció szociális háttere. Orvosi Hetilap 2002; 143; 1985-90
24. Siqueira FM., Cota LO., Costa JE., Haddad JP., Lana AM., Costa FO.: Intrauterine growth restriction, low birth weight, and preterm birth: adverse pregnancy outcomes and their association with maternal periodontitis. J Periodontol 2007 Dec; 78; 2266-76

25. Gibbs RS. The relationship between infections and adverse pregnancy outcomes. An overview. Annals of Periodontology 2002; 6; 153-163.

26. Hill GB.: Preterm birth: Associations with genital and possibly oral microflora. Annals of Periodontology 1998; 3; 222-232.

27. E. Urbán, M. Radnai, T. Novák, I. Gorzó, A. Pál, E. Nagy.: Distribution of anaerobic bacteria among pregnant periodontitis patients who experience preterm delivery. Anaerobe 2006; 12; 52-57

28. Hillier SL., Witkin SS.., Krohn MA, Watts DH., Kiviat NB., Eschenbach DA.: The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstetric and Gynecology 1993; 81; 941-948

29. Jeffcoat MK. et al.: Periodontal infection and preterm birth. Results of a prospective study. Journal of the American Dental Association 2001; 132; 875-880.

30. McGaw T.: Periodontal disease and preterm delivery of low-birth-weight infants. Journal of the Canadian Dental Association 2002; 68; 165-169

31. Holbrook WP., Óskarsdóttír Á., Fridjónsson T., Einarsson H., Hauksson A., Geirsson RT.: No link between low-grade periodontal disease and preterm birth; a pilot study in a healthy Caucasian population. Acta Odontol Scand 2004; 62; 177-179

32. Mitchell-Lewis D., Engebretson SP., Chen J., Lamster IB., Papapanou PN.: Periodontal infection and pre-term birth: early findings from a cohort of young minority women in New York. Eur J Oral Sci 2001; 109; 34-39

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X. Appendix. Detailed publications related to the thesis