UNIVERSIDADE FEDERAL DO RIO DE JANEIRO
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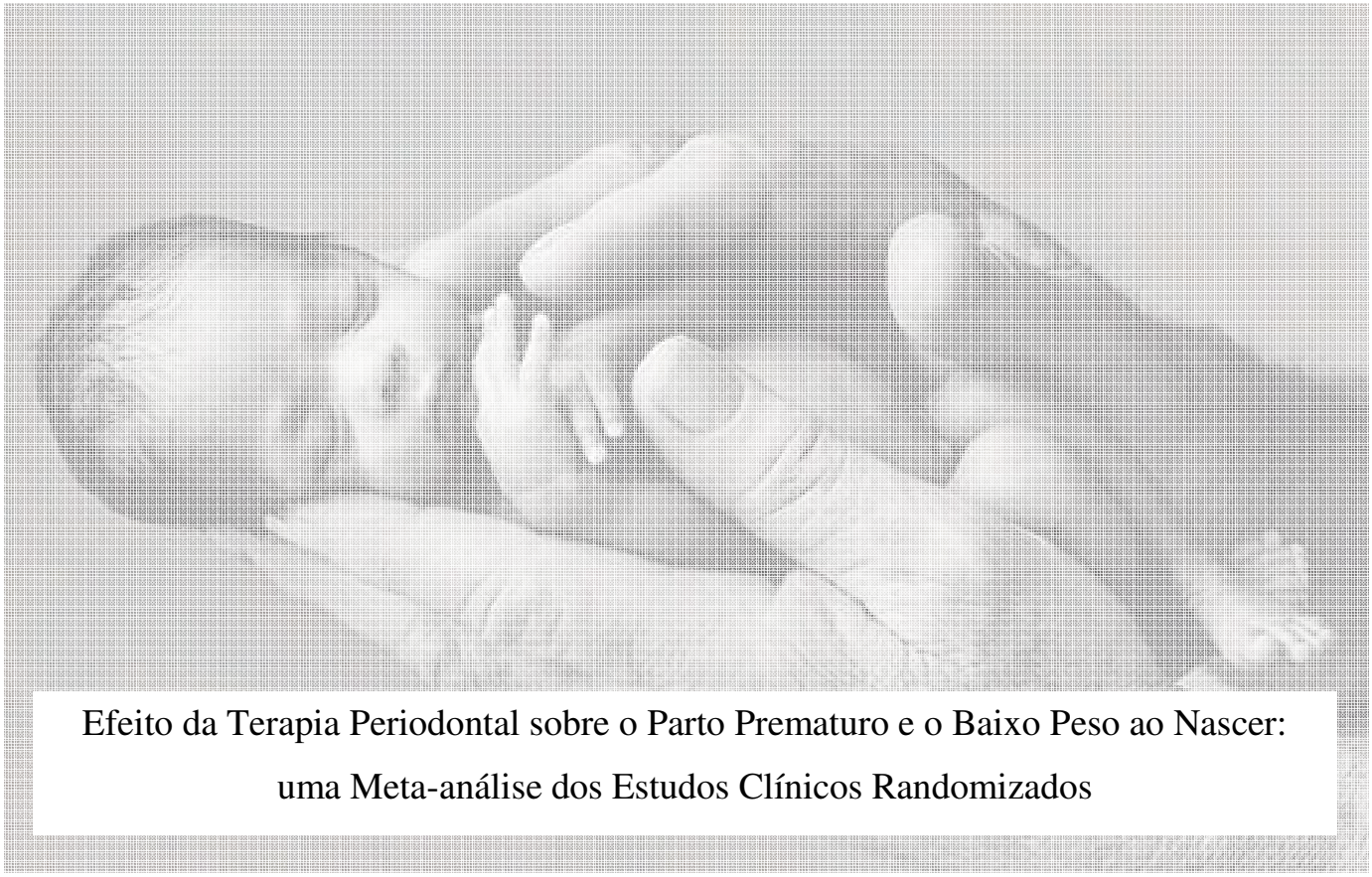

# Efeito da Terapia Periodontal sobre o Parto Prematuro e o Baixo Peso ao Nascer: uma Meta-análise dos Estudos Clínicos Randomizados

Rio de Janeiro
2009

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Odontologia (Periodontia), Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do Grau de Mestre em Odontologia (Periodontia).

Orientadores:

Prof[a]. Dr[a]. Anna Thereza Thomé Leão

Prof. Dr. Mario Vianna Vettore

Rio de Janeiro
2009

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Mariana Fampa Fogacci

Dissertação de Mestrado submetida ao Programa de Pós-Graduação da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do Grau de Mestre, sob orientação dos professores Anna Thereza Thomé Leão e Mario Vianna Vettore.

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2009

**FICHA CATALOGRÁFICA**

Fogacci, Mariana Fampa. **Efeito da Terapia Periodontal sobre o Parto Prematuro e o Baixo Peso ao Nascer: uma meta-análise dos Estudos Clínicos Randomizados.** Rio de Janeiro, 2009 / Mariana Fampa Fogacci.
xiii, 33p.

Dissertação (Mestrado em Odontologia/Periodontia) – Universidade Federal do Rio de Janeiro, Faculdade de Odontologia/Periodontia, 2009.

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1. Terapia Periodontal; 2. Parto Prematuro; 3. Baixo Peso ao Nascer; 4. Revisão Sistemática

I.Anna Thereza Thomé Leão (orient.); Mario Vianna Vettore (orient.). II. Universidade Federal do Rio de Janeiro. Faculdade de Odontologia. Pós-Graduação em Odontologia/Periodontia. III. Título

CDD

Aos meus pais, Nelson e Myriam, meus grandes incentivadores...

Ao meu irmão, Daniel, amigo antes de qualquer coisa...

Ao meu noivo, Davi, o meu grande amor e o meu oásis...

… dedico…

## AGRADECIMENTOS

Em primeiro lugar a Deus, pela certeza de que sempre guia meu caminho.

Aos meus pais, Nelson e Myriam, pelo amor, carinho, apoio e compreensão em todos os momentos e pelo constante incentivo a todos os meus sonhos profissionais.

Ao Daniel pela alegria de, além de sermos irmãos, sermos amigos antes de tudo.

Ao Davi, pelo amor que se iniciou durante o curso de Mestrado, por tudo o que representa pra mim, pela alegria da convivência, pela admiração pessoal e profissional, por contribuir para eu me tornar uma pessoa melhor, pela paixão, pelo carinho, pela felicidade de saber que ele está ao meu lado, sentimentos que se multiplicam a cada dia. Te amo!

À minha querida orientadora, Profa. Anna Thereza, por todas as oportunidades! Por ter me incentivado sempre, desde que a conheci no quarto período da minha graduação, até hoje! Pelos ensinamentos não só profissionais, mas de vida, pela sua dedicação ao seu trabalho e aos seus alunos, pelo exemplo de pesquisadora, pela amizade, pelo carinho, pelo sorriso largo e constante e pela agradável convivência!

Ao meu orientador, Prof. Mario, pelos ensinamentos transmitidos, pelas críticas construtivas, pela paciência e pela experiência em pesquisa compartilhada.

À Cristine, de quem fui aluna de iniciação científica, pela amizade construída, pelo exemplo e inspiração que me motivaram ainda mais a seguir este caminho e chegar até este momento.

Aos professores do curso, Eduardo e Carmelo, pelos ensinamentos divididos, pelo apoio e atenção.

À professora Cynésia, por tudo que aprendi desde a graduação até hoje, pelas oportunidades, pelo exemplo de organização e dedicação ao seu trabalho.

À Liana, pela amizade, pela presença constante e pelas angústias e felicidades divididas desde a época da seleção para o curso até agora! Por todas as vezes em que estava mais nervosa do que eu, mas encontrou maneiras de me ajudar a me acalmar!

A todos os colegas de curso com os quais convivi durante esses dois anos, em especial Mayra, Paola, Vivi e Melina pela simpatia que tenho por vocês e pela amizade, que crescem a cada dia.

À Katia, pela amizade dos tempos de escola que permanece até hoje, pela compreensão, pelo apoio e por se alegrar com minhas conquistas!

Á Juliana e à Silvia, pelo apoio, pela amizade, pelos pensamentos positivos e por estarem sempre me incentivando!

À Tia Arlene e à Gilda pelo carinho, pela amizade e por torcerem por mim!

A todos os meus amigos e familiares que torcem por mim e entenderam minhas ausências!

*Time Of Your Life* *O Tempo De Sua Vida*

Green Day

| | |
|---|---|
| Another turning point | Outro momento decisivo |
| a fork stuck in the road | Uma bifurcação cravada na estrada |
| Time grabs you by the wrist | O tempo te agarra pelo pulso e |
| directs you where to go | te mostra aonde ir |
| So make the best of this test | Então, dê o seu melhor nesse teste |
| and don't ask why | e não pergunte por que |
| It's not a question | Essa não é uma pergunta, |
| but a lesson learned in time | Mas sim uma lição que se aprende na hora certa |
| | |
| It's something unpredictable | É algo imprevisível |
| but in the end it's right | mas no final é certo |
| I hope you had the time of your life | Espero que você tenha curtido o tempo de sua vida |
| | |
| So take the photographs | Então pegue as fotografias |
| and still frames in your mind | e as imagens dispersas em sua mente |
| Hang it on a shelf | Coloque-as na prateleira |
| of good health and good time | da boa saúde e dos bons tempos |
| Tattoos of memories | Tatuagens de memórias |
| and dead skin on trial | e pele morta em julgamento |
| For what it's worth | O que vale a pena |
| it was worth all the while | Valeu durante todo o tempo |
| | |
| It's something unpredictable | É algo imprevisível |
| but in the end it's right | mas no final é certo |
| I hope you had the time of your life | Espero que você tenha curtido o tempo de sua vida |

**RESUMO**

O objetivo deste estudo foi conduzir uma meta-análise dos ensaios clínicos randomizados que avaliaram o efeito da terapia periodontal na prematuridade (PP) e baixo peso ao nascer (BPN). A doença periodontal tem sido proposta como fator de risco para o PP e o BPN. O efeito da terapia periodontal sobre esses desfechos não está bem estabelecido. A pesquisa foi conduzida de forma sistemática nas bases de dados PubMed, Bireme, Lilacs e Cochrane. Apenas ensaios clínicos randomizados foram incluídos. A busca resultou em 11 estudos. Sete artigos preencheram os critérios de inclusão para o desfecho PP e quatro meta-análises foram realizadas de acordo com critérios diferentes: (a) profundidade de sondagem e perda de inserção para definição de periodontite, RR = 0,58 (IC95% 0.29-1.12) (quatro estudos), (b) controle para multiparidade, RR = 0,77 (IC95% 0.55-1.07) (cinco estudos), (c) controle para PP anterior, RR = 0,75 (IC95% 0.51-1.10) (cinco estudos), e (d) controle para infecções do trato geniturinário, RR = 0,75 (IC95% 0.57-1.05) (seis estudos). Outra meta-análise para PP foi realizada considerando-se todos os critérios acima (três estudos), RR = 0,63 (IC95% 0.32-1.22). BPN foi considerado em dois estudos, em que os quatro critérios acima foram satisfeitos, RR = 0,52 (IC95% 0.10-2.60). Não há, portanto, evidências que suportem um real efeito do tratamento periodontal na diminuição do PP e BPN.

**ABSTRACT**

A meta-analysis of the randomized clinical trials that evaluated the effect of periodontal therapy on preterm birth (PTB) and low birth weight (LBW) was conducted. Periodontal disease has been proposed as a risk factor for PTB and LBW. The effect of periodontal therapy on those outcomes is not well established. A systematically search was conducted at PubMed, Bireme, LILACS and Cochrane databases. Only randomized clinical trials were included. The search resulted in 11 studies. Seven papers met the inclusion criteria for PTB outcome and four meta-analysis were performed according to different criteria: (a) probing depth and attachment loss for periodontitis definition, RR=0.58 (CI95% 0.29-1.12) (four studies), (b) controlling for multiparity, RR=0.77 (CI95% 0.55-1.07) (five studies), (c) controlling for previous PTB, RR=0.75 (CI95% 0.51-1.10) (five studies), and (d) controlling for genitourinary infections, RR=0.75 (CI95% 0.57-1.05) (six studies). Another meta-analysis for PTB was conducted considering all the above criteria (three studies), RR=0.63 (CI95% 0.32-1.22). LBW was considered in two studies, in which the four above criteria were met, RR=0.52 (CI95% 0.10-2.60). There is no evidence to support a real effect of the periodontal therapy in the reduction of PTB and LBW.

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**LISTA DE SIGLAS E ABREVIATURAS**

AIDS : Acquired Immune Deficiency Syndrome

AL : Attachment Loss

BOP : Bleeding on Probing

BPN : Baixo Peso ao Nascer

CI : Confidence Interval

CIUR : Crescimento Intrauterino Restrito

CONSORT : Consolidated Standards of Reporting Trials

CRH : Hormônio Liberador de Corticotropina

HIV : Human Immunodeficiency Virus

IL-1 : Interleucina 1

LBW : Low Birth Weight

*p* : Valor de p

PD : Probing Depth

PGE-2 : Prostaglandina E2

PLBW : Preterm Low Birth Weight

PROPHY : Prophylaxis

PP : Parto Prematuro

PTB : Preterm Birth

PTLBW : Preterm Low Birth Weight

RCT : Randomized Clinical Trials

RL : Radicais Livres

RR : Relative Risk

SRP : Scaling and Root Planing

TNF – α : Fator de Necrose Tumoral

**SUMÁRIO**

## 1. INTRODUÇÃO

O parto prematuro (PP) e o baixo peso ao nascer (BPN) são desfechos adversos da gestação, caracterizados pelo nascimento de crianças com menos de 37 semanas completas de idade gestacional e peso inferior a 2500g (WHO, 2007). São problemas não resolvidos na medicina perinatal, associados ao aumento na morbidade e mortalidade infantil a curto e longo prazo, bem como ao desenvolvimento de anormalidades cognitivas e de comportamento, problemas que persistem até a idade adulta (Kliegman, 1990; Barker, 1993; UNICEF, 2004). Essas conseqüências geram elevado custo para os serviços de saúde em decorrência da assistência neonatal requerida e do seguimento especializado após a alta hospitalar (Petrou, 2003). Além disso, no mundo há aproximadamente 13 milhões de PP por ano e mais de 20 milhões de crianças com BPN (UNICEF, 2004). Portanto, há grande interesse na pesquisa de fatores etiológicos do PP e BPN para que medidas preventivas e intervenções possam reduzir a ocorrência desses desfechos gestacionais (Michalowicz *et al*., 2007).

A fisiopatologia do parto prematuro abrange alguns mecanismos básicos que resultam no desenvolvimento de contrações uterinas e início do trabalho de parto: a) inflamação local que promove a liberação de endotoxinas locais ou citocinas inflamatórias, como o fator de necrose tumoral (TNF-α) e a interleucina-1 (IL-1); b) estresse fetal ou materno que provoca a liberação de hormônios hipotalâmicos e adrenais, como ocitocina, cortisol e hormônio liberador de corticotropina (CRH); c) modificações físicas locais (como fetos gemelares) que promovem a liberação de ocitocina e CRH; d) a redução do fluxo sanguíneo placentário que leva ao crescimento fetal intrauterino restrito, e produz dano tecidual por meio de peroxidases lipídicas e radicais livres; e) hemorragia tecidual que leva à insuficiência vascular uteroplacentária por meio do aumento da liberação de CRH. A liberação de algumas dessas substâncias mencionadas causa a ocorrência de contração uterina (Freitas *et al*., 2006).

O nascimento de bebês com baixo peso é resultado do parto prematuro ou do crescimento fetal intrauterino restrito (CIUR) (Ohlsson *et al*., 2008). O CIUR não é uma doença específica, mas a manifestação de muitos distúrbios fetais, placentários e maternos (Freitas *et al*., 2006). Dentre os principais, temos: alterações genéticas ou cromossômicas; infecções fetais; gestações múltiplas; intervalo entre as gestações inferior a dois anos; insuficiência vascular uteroplacentária; transtornos da nutrição materna; baixa escolaridade materna; uso de drogas (tabaco, álcool, drogas ilícitas); doenças maternas (doença renal crônica, hipertensão crônica, hiperinsulinemia, anemia, infecção do trato urinário, doença auto-imune) (Freitas *et al*., 2006).

Nesse contexto, a doença periodontal tem sido proposta como um possível fator de risco para o PP e o BPN, por se tratar de uma doença de natureza crônica, inflamatória e infecciosa, que age como um reservatório de bactérias anaeróbicas gram-negativas, lipopolissacarídeos e citocinas, como prostaglandinas (PGE2) e TNF- α, sendo considerada uma possível ameaça para a unidade fetoplacentária (Collins *et al*., 1994 a-b).

No entanto, não há um consenso na literatura sobre a possível associação entre a infecção periodontal e o PP e/ou BPN, bem como não está determinado se essa relação é causal ou coincidência (Vettore *et al.*, 2006).

A grande dificuldade em se esclarecer essas questões reside no fato de haver vários fatores de risco para o PP e o BPN que são comuns à doença periodontal (Kramer, 1987; Vettore *et al*. 2006). Os estudos epidemiológicos nesta área precisam controlar todos os potenciais fatores de confusão e ainda manter um tamanho de amostra satisfatório. Observa-se que em alguns estudos as gestantes que tem esses fatores não são excluídas, mas no momento da análise dos dados são conduzidas análises multivariadas, a fim de conseguir esse controle.

A quantidade de pesquisas sobre a possível associação da doença periodontal com os desfechos adversos da gravidez é considerável e continua aumentando, apesar de toda a dificuldade citada. Meta-análises dos estudos de associação foram conduzidas, e identificaram inúmeros trabalhos com falhas metodológicas graves, critérios de inclusão e exclusão diversos, tamanhos de amostra e critérios de classificação de doença periodontal diferentes (Xiong *et al*. 2006; Vettore *et al*. 2006; Vergnes *et al*. 2007).

Apesar de as meta-análises de estudos observacionais não conseguirem apresentar uma conclusão sobre o assunto devido às disparidades entre os trabalhos de associação, estudos intervencionais têm sido realizados a fim de definir se o tratamento periodontal reduz a incidência de PP e BPN. Recentemente, uma meta-análise desses estudos (Polyzos *et al*., 2009) concluiu que o tratamento da doença periodontal com raspagem e alisamento radicular durante a gravidez reduziu a incidência desses desfechos. No entanto, potenciais falhas metodológicas foram detectadas, o que possivelmente superestimou os resultados.

Diante da quantidade de pesquisas nesse assunto, a realização de revisões sistemáticas e meta-análises bem conduzidas é fundamental para se reunir de forma criteriosa as evidências existentes e delinear conclusões sobre a associação entre a doença periodontal e o PP e o BPN.

## 2. PROPOSIÇÃO

O presente estudo consiste de uma meta-análise conduzida para responder à seguinte pergunta: O tratamento periodontal em gestantes reduz a incidência de parto prematuro e baixo peso ao nascer?

## 3. DELINEAMENTO DA PESQUISA

O primeiro trabalho produzido foi uma Carta ao Editor do periódico Journal of Dental Research, sobre um estudo clínico randomizado recentemente publicado (Radnai et al. 2009). Durante a revisão de literatura sistemática conduzida para realização da meta-análise, verificou-se a recente publicação desse estudo, que afirma em suas conclusões que mulheres com parto prematuro ameaçado e periodontite crônica incial localizada tinham significativamente menos chances de desfechos adversos da gestação se recebessem tratamento periodontal antes da 35ª semana gestacional. Concluíram ainda que seus achados fornecem evidências indiretas para se assumir que a periodontite materna pode causar parto prematuro. A leitura e avaliação criteriosas do mesmo nos permitiram verificar algumas questões metodológicas importantes, como a ausência do controle para variáveis de confusão, o critério de classificação de doença periodontal inapropriado e a média de profundidade de sondagem inicial pequena para o grupo tratamento. Por essas razões, uma carta ao editor foi elaborada e submetida.

O segundo trabalho teve por objetivo a realização de uma revisão sistemática sobre o efeito do tratamento periodontal nos desfechos adversos da gravidez. Essa pesquisa iniciou-se por uma busca sistemática dos estudos clínicos randomizados sobre o assunto nas bases de dados: PubMed, Bireme, LILACS and Cochrane, que foi realizada de março a maio de 2009 por três pesquisadores. Foram identificados 81 estudos, dos quais somente sete atenderam aos critérios de inclusão definidos inicialmente. Esses sete estudos foram avaliados de acordo com a definição de doença periodontal e o controle de possíveis variáveis de confusão. Quatro meta-análises foram realizadas com os estudos que atenderam a cada um desses critérios. Em seguida, uma última meta-análise foi realizada somente com os estudos que atenderam aos quatro critérios ao mesmo tempo.

## 4. TRABALHOS SUBMETIDOS

Trabalho 1 - **"Letter to the Editor : Benefits of Periodontal Therapy When Preterm Birth Threatens"**, submetido ao periódico Journal of Dental Research.

Trabalho 2 – **"The Effect of Periodontal Therapy on Preterm Low Birth Weight: a Meta-Analysis of Randomized Clinical Trials"**, a ser submetido ao periódico Journal of Periodontal Research.

## 4.1 TRABALHO 1

**The Editor,**

The article by Radnai *et al*., 2009 concluded that periodontal treatment completed before the 35th week of pregnancy appeared to have a beneficial effect on birthweight and time of delivery (PTLBW). However, this study has three major shortcomings: 1. The authors have failed to control for confounding variables. Multiparity (Kramer, 1987; Vettore *et al*., 2008), one of the major risk factors for PTLBW, tended to be higher in the control group compared to test group. Similarly, 'Educational Level of Mothers' and 'Occupation of Fathers' showed a borderline difference between groups. So, a multivariate analysis should have been performed to assess the association between periodontal disease and PTLBW. 2. Another shortcoming is the inappropriateness of their criteria for classifying periodontal disease: at least at one site with ≥4 mm probing depth and bleeding on probing (BOP) at ≥50% of teeth. Probing depth is not sufficient to distinguish between periodontitis and gingivitis. In addition, pregnant women are more prone to have gingivitis and gingival enlargement. That is often associated with pseudopockets (≥4 mm). It has been demonstrated that criterion used affects the relationship between periodontal status and PTLBW (Manau *et al*., 2008). 3. The treatment group had a mean probing depth of 2.11 mm. Such a small initial mean probing depth is unlikely to significantly alter levels of circulating cytokines to affect PTLBW. Therefore treatment would not reduce the risk of the mother having a preterm baby. This letter proposal is discussing the subject, based on the comments made here.

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**References**

1. Kramer MS (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ* 65:663-737.

2. Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ (2008). Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol* 35:385–397.

3. Radnai M, Pál A, Novák T, Urbán E, Eller J, Gorzó I (2009). Benefits of Periodontal Therapy When Preterm Birth Threatens. *J Dent Res* 88(3 Suppl):280-284.

4. Vettore MV, Lamarca GA, Leão ATT, Thomaz FB, Sheiham A, Leal MC (2006). Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies. *Cad Saude Publica* 22(10 Suppl): 2041-53.

## 4.2 TRABALHO 2

# The Effect of Periodontal Therapy on Preterm Low Birth weight: a Meta-Analysis of Randomized Clinical Trials

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Keywords : periodontal therapy, preterm birth, low birth weight, systematic review.

**Abstract**

Objective: A meta-analysis of the randomized clinical trials that evaluated the effect of periodontal therapy on preterm birth (PTB) and low birth weight (LBW) was conducted.

Background Data: Periodontal disease has been proposed as a risk factor for PTB and LBW. The effect of periodontal therapy on those outcomes is not well established.

Methods: A systematically search was conducted at PubMed, Bireme, LILACS and Cochrane databases. Only randomized clinical trials were included.

Results: The search resulted in 11 studies. Seven papers met the inclusion criteria for PTB outcome and four meta-analysis were performed according to different criteria: (a) probing depth and attachment loss for periodontitis definition, RR=0.58 (CI95% 0.29-1.12) (four studies), (b) controlling for multiparity, RR=0.77 (CI95% 0.55-1.07) (five studies), (c) controlling for previous PTB, RR=0.75 (CI95% 0.51-1.10) (five studies), and (d) controlling for genitourinary infections, RR=0.75 (CI95% 0.57-1.05) (six studies). Another meta-analysis for PTB was conducted considering all the above criteria (three studies), RR=0.63 (CI95% 0.32-1.22). LBW was considered in two studies, in which the four above criteria were met, RR=0.52 (CI95% 0.10-2.60).

Conclusion: There is no evidence to support a real effect of the periodontal therapy in the reduction of PTB and LBW.

**Introduction**

Preterm birth (PTB) and low birth weight (LBW) are adverse pregnancy outcomes characterized by newborn with less than 37 weeks of gestational age and weighing less than 2,500g at birth (1).

The PTB remains an unsolved problem in Perinatal Medicine. In the world, there is approximately 13 millions of PTB per year, representing the major obstetric challenge. PTB is of significant public health importance because of its association with an increase in infant mortality and with childhood morbidities in a short or long term, such as developmental problems, cerebral palsy, hearing and visual impairments, and an increased risk of sudden infant death (2,3). Premature children also have higher risk of developing cognitive abnormalities, such as learning difficulties, and behavioral abnormalities and problems that persist to adulthood (2,3). Therefore, there is a great concern that PTB rate is increasing in some countries (2).

The birth of babies with LBW is the result of premature birth or intrauterine restricted fetal growth (4). Poor growth during the intrauterine period increases the risks of perinatal and infant mortality and morbidity throughout the life (3-5). LBW is a multicausal problem that may result in a wide spectrum of diseases in later life such as hypertension, ischemic heart disease (6), stroke, metabolic syndrome, diabetes, malignancies, osteoarthritis, and dementia (7,8), as also in the inhibition of cognitive development and growth. In the world, there are more than 20 million children with LBW, 15.5% of all live births. The prevalence of LBW in developing countries (16.5%) is more than twice than in developed regions (7%) (2).

There are several risk factors for premature delivery: multiple gestations, placental abnormalities, smoking, diabetes mellitus, vaginal infections, previous PTB, immunological diseases, previous abortion, multiparity, maternal age (<17 years or >35 years), ethnicity, low socio-economic status, alcohol abuse, drugs use during pregnancy, inadequate prenatal care, psychological factors, type of maternal work during pregnancy (4,9,10).

Risk factors for LBW can be classified in three groups. (a) Maternal Factors: age (<17 years or > 35 years), initial weight below 54 kg, cardiovascular adaptation, darker-skinned black ethnicity, lower schooling, inappropriate work, poor nutritional status, smoking, alcohol abuse, drug use, use of teratogenic drugs, anticoagulants and hydantoin, poor adaptation of the maternal circulation, chronic kidney disease, preeclampsia, chronic hypertension, hyperinsulinaemia, chronic cardiopulmonary disease, anemia, genito-urinary infection, autoimmune disease; (B) Fetal Factors: female gender, chromosomal abnormalities, dysplasias, osteogenesis imperfecta, placental sulfatase deficiency, neural tube defects, radiation exposure,

intra-uterine infection; and (C) Uteroplacentary Factors: bicornuate uterus, abnormal insertion of cord, single umbilical artery, placental mosaic and abnormality of implantation site (4,9,10,11).

Maternal periodontal disease has been proposed as another risk factor for PTB and/or LBW. As known, infections with acute inflammatory response are the main causes of PTB. A significant proportion of the inflammation associated with PTB is attributed to intrauterine infection (12, 13) and conditions such as bacterial vaginosis, which affects around 40% of cases of PTB (14,15).

Periodontitis has a chronic inflammatory infectious nature and act as a reservoir of anaerobic gram-negative microorganisms, lipopolissacharides and cytokines, including PGE2 and TNF- α, therefore, can be considered a threat to the fetoplacentary unit (16, 17).

It has been suggested that the increase of cytokines and local mediators of inflammation, such as PGE2 and TNF- α, caused by release of endotoxins and lipopolysaccharides by microorganisms related to periodontal disease increase the levels of the systemic inflammatory mediators, which initiate the intrauterine inflammation, leading to premature labor, and therefore, the premature delivery (18). Another possibility could be the hematogenous spread of microorganisms related to periodontal disease causing chorioamniotic infections that can lead to premature delivery (18,19,20) although the exact mechanism was not well established (18).

The molecular mechanisms in which PGE2 and TNF- α could induce LBW are also unknown, but certain theories have been proposed. It has been suggested that bacterial products stimulate the monocyte/macrophage cells to produce cytokines like TNF- α that initiate parturition by stimulating the intrauterine tissues to produce prostaglandins (21). It is documented that TNF- α causes ischemic necrosis of certain solid tumors (22), and there is an analogy to the feto-placental unit as an external tumor. Thus, some of the placental pathology associated with LBW may be a result of TNF- α challenge. Finally, it has been shown that TNF- α prevents lipid uptake and utilization. So, it is possible that TNF- α can provoke intrauterine growth restriction through a selective induced nutrient deprivation to the fetus (17).

In literature, there is no consensus on the possible relationship between periodontal infection and PTB and/or LBW (10) and it is not determined whether these possible relationships are causal or coincidence.

Some non systematic reviews concluded that more studies with better methodological quality are necessary to confirm if periodontitis in pregnant women is an independent risk factor for adverse pregnancy outcomes (23,24,25). Some inconsistencies in the case-control and cohort studies are on how periodontal disease and pregnancy outcomes were defined and measured. The definitions of maternal periodontitis employed varied significantly and over 14 definitions

have been used. In addition, different clinical parameters of periodontitis as well as measures thresholds were employed. The undesirable pregnancy outcomes investigated were not consistent as well, including gestational age at birth less than 37 weeks and 32 weeks, PTB or LBW, PTB and LBW, preterm labor, or premature rupture of membranes. Although gestational age at birth and birth weight are generally correlated, the risk factors for these conditions are not the same and the use of composite undesirable birth outcomes may resulted in invalid findings.

Most of the non systematic reviews concluded that there is insufficient evidence for health care policy recommendations to provide periodontal screening and treatment for pregnancies to reduce the risk of adverse pregnancy outcomes (23,24,25). However, some non systematic reviews concluded that periodontal disease is a risk factor for PTB and LBW (26,27,28). Since these reviews were not conducted in a systematic way, several methodological flaws might have affected their findings.

Similarly, systematic reviews and meta-analysis on the relationship between maternal periodontitis and preterm LBW have been providing conflicting results. A meta-analysis of 17 studies concluded that periodontal disease was an independent risk factor for preterm LBW (29). However, the combined value seemed to overestimate the real value of the association between periodontitis and PLBW, since studies with important methodological differences had their results pooled. Indeed, there was a clear and inverse trend between the quality of the studies and the strength of association.

Xiong et al. (30) reported that evidence of an association between periodontal disease and risk factor for increased PLBW occurs especially in economically disadvantaged populations, but potential biases and limited number of randomized controlled clinical trials (RCT) prevent us from reaching a clear conclusion. They reported that more studies were needed to examine potential associations between periodontal disease and the increased risk for pre-eclampsia, gestational diabetes, early interruption of pregnancy and intrauterine growth restriction.

Vettore et al. (10) concluded that the serious methodological limitations of most studies raise doubts about their findings. They do not draw appropriate conclusions about the true association between periodontal disease and adverse outcomes of pregnancy. There is no scientific justification to recommend the resolution of periodontal disease in pregnant women as a means of reducing such outcomes.

Recently, a meta-analysis (31) of RCT concluded that periodontal disease treatment with scaling and/or root planning during pregnancy reduced the incidence of PTB or LBW. However, potential methodological flaws were detected that have potentially overestimated their results.

Periodontal disease definition varied significantly among studies and in some analysis gingivitis was grouped with periodontitis. In addition, some analysis included studies that did not control for confounders such as multiparity, previous PTB and genitourinary infections. So, the pooled estimative obtained when studies with such methodological differences were grouped are biased and should be interpreted very carefully.

This systematic review was conducted to answer the following question: is there beneficial effect of periodontal treatment in the reduction of PTB and LBW incidence?

## Materials and Methods

A systematic search of studies was performed in PubMed, Bireme, LILACS and Cochrane databases. The following descriptors were used: (low birth weight, pre term, preterm, premature, immature) OR (labor, pregnancy, birth, neonatal, fetal, intrauterine) AND (complication, disease, adverse, PLBW) AND (periodontal) AND (treatment). The limits were: clinical trials, RCT, reviews. The search strategy was supplemented by checking the references of the previous review articles.

The inclusion criteria consisted of clinical trials, randomized clinical trials or controlled clinical trials that considered the treatment of destructive periodontal disease/periodontitis as the intervention of the interest. Only papers written in English language were included. The exclusion criteria were cohort studies, case-control studies, cross-sectional studies, editorial letters, historical/narrative reviews and descriptive studies such as case reports and case series.

The studies were evaluated according to Consolidated Standards of Reporting Trials (CONSORT) statement (32). All sections of papers were analyzed: Title and Abstract, Introduction, Methods, Results and Discussion. Each section was subdivided in items:

**Introduction**: 1. Evidence of benefits; 2. How intervention might work; 3. Justify need for a new trial; 4. Reference previous trials or absence; 5. Nature, scope and severity of the problem.

**Methods**: 1. Participants (1a. Eligibility criteria – Inclusion/Exclusion criteria; 1b. Settings and locations); 2. Interventions (2a. Intervention group; 2b. Control group); 3. Maintenance therapy; 4. Objectives; 5. Outcomes (5a. Primary and secondary; 5b. Quality of measurements); 6. Sample size (6a. How sample was determined; 6b. Interim analyses/stopping rules); 7. Randomization (7a. Method to generate sequence; 7b. Details of any restriction; 7c. Allocation concealment; 7d. Implementation); 8. Blinding; 9. Statistical methods.

**Results**: 1. Participant flow (1a. Flow of participants; 1b. Deviations); 2. Recruitment (2a. Recruitment; 2b. Follow-up); 3. Baseline data; 4. Numbers analyzed; 5. Outcomes and estimation; 6. Ancillary analyses; 7. Adverse events.

**Discussion**: 1. Interpretation (1a. Key findings; 1b. Mechanisms/explanations; 1c. Comparison with other studies; 1d. Limitations; 1e. Clinical/research implications); 2. Generalizability; 3. Overall evidence.

Besides those items we included the following: Diagnosis of periodontal disease; Calibration; Confidence Interval. The diagnosis of periodontal disease used was important for recognizing and grouping studies that included women with similar periodontal characteristics; adequate calibration is an important parameter to verify internal validity of studies; and confidence interval was important to be extracted together with the association measure used.

For each item of the CONSORT checklist, the article was scored as *adequate* or *inadequate*. When the information was not available, the paper was classified as *unclear*.

Finally, the relative risk (RR) and 95% confidence interval (CI) was extracted for each study for PTB and LBW.

In order to obtain unbiased estimative of associations between periodontal disease treatment and PTB/LBW separate analysis were performed according to the outcome of interest, the periodontal disease definition and the control for confounders. The first five analyses referred to PTB and the sixth involved RCTs for LBW as the outcome. For the first analyses, only papers that used probing pocket depth and attachment loss measures as the criteria for periodontitis' definition were included. Papers that used only attachment loss for the definition of periodontal disease were excluded, since that parameter measures accumulated past disease rather than current periodontal disease activity (33). We have considered that using only that parameter in the inclusion criteria of women could result in treating women without current disease, generating some bias. Therefore, treatment would not reduce the risk of the mother having a preterm baby. In addition, papers that used probing depth as the unique parameter for periodontal disease definition were excluded, since probing depth is not sufficient to distinguish between periodontitis and gingivitis. Pregnant women are more prone to have gingivitis and gingival enlargement, which is often associated with pseudopockets (≥4 mm).

A second analysis was then done using the following criteria: have the studies controlled the confounding variable multiparity (9,10) for PTLBW? Studies were excluded if they have not mentioned information about this confounder or did not found significant difference between control and treatment groups for that variable, with a p value>0.05 but <0.20, and did not do a

multivariate analysis. When the p value is included in that interval, performing a multivariate analysis is recommended in order to adjust for the variable (34).

In a third analysis, were included studies that have controlled for previous PTB. Again, were excluded papers that did not mentioned controlling for that variable, or did not performed multivariate analysis when the p value was >0.05 but <0.20. Probably the most consistent predictor of PTB is the occurrence of previous PTB (24, 35). In a study of Swedish women, those who had at least one previous preterm delivery at <32 weeks were nine times more likely to deliver again at <32 weeks (36).

A fourth criteria was considered in order to produce another analysis: have the studies controlled for an important risk factor for preterm birth (9,10) as genitourinary infection? Papers were excluded if they have not controlled for that variable (not mentioning it or not performing multivariate analysis).

In a fifth analysis, we joined only studies that had all of the above mentioned characteristics (probing depth and attachment loss measures and control for multiparity, previous PTB and infections).

The last analysis was on LBW and all previous criteria were applied to select the studies for meta-analysis.

In the present study distinct meta-analysis using random effects model were performed for each analysis described above, in order to obtain reliable and unbiased pooled estimative of studies that were methodologically similar concerning the periodontal disease definition and the control for confounders. Chi-square tests for heterogeneity was done to verify the homogeneity among the selected studies and if their results could be pooled.

All statistical analyses were performed using commercial statistical software, version STATA 10.0 (Strata Corp, TX, USA). The significance level that was established for analyses was 5% ($P \leq 0.05$).

**Results**

The initial search resulted in 81 articles, of which 11 were clinical studies: Radnai et al., 2009 (38); Radnai et al 2008 (39); Novak et al., 2008 (40); Tarannum et al., 2007 (41); Gazolla et al., 2007 (42); Offenbacher et al., 2006 (43); Michalowicz et al., 2006 (44); Sadatmansouri et al., 2006 (45); López et al., 2005 (46); Jeffcoat et al., 2003 (47); López et al., 2002 (19). Of those papers, four were excluded due to different reasons: one was published in Hungarian

language (39), one was a duplicate paper (40) of Michalowicz et al., 2006 study, one was a non randomized clinical trial (42), and one analyzed the influence of the treatment of gingivitis on the incidence of PTB (46).

The seven remaining papers were classified accordingly to CONSORT check-list. The 16 most important items are described in Table 1. Randomization was performed in all studies selected, for exclusion criteria most of them excluded women with systemic problems, twin pregnancies and tobacco users. Calibration was done by the majority of studies, but the sample size, the numbers analyzed were much different among them.

The periodontal treatment offered to intervention and control groups were also analyzed as well as the procedures of maintenance therapy (Table 2). In all studies, all participants of the intervention group received instructions for dental plaque control, supragingival scaling and scaling and root planning. Other procedures as prophylaxis and 0.12% chlorhexidine mouthrinse twice daily were offered for intervention group at some studies only. For control group, the majority of studies offered no treatment at all, but plaque instructions, prophylaxis and supragingival scaling were performed in a few studies.

In order to obtain valid estimative of associations between periodontal disease treatment and preterm LBW separate meta-analysis were performed according to the outcome of interest, the periodontal disease definition and the control for confounders (Figure 1).

As only two studies (44, 19) had both PTB and LBW as outcomes, we first combined results for PTB (Figure 2), which was the outcome for most studies.

For the first analyses, were excluded two studies that used only attachment loss for the definition of periodontal disease (Tarannum et al.: ≥ 2mm AL at ≥ 50% of examined sites; Jeffcoat et al.: at least 3 sites with AL ≥ 3mm). Another paper was also excluded from the analysis since it included subjects using the parameters probing depth and bleeding on probing (Radnai et al.: ≥ 4 mm PD, at least at one site, and BOP for ≥ 50% of teeth). Remaining papers (Offenbacher et al., Michalowicz et al., Sadatmansouri et al., López et al.) used both probing depth and attachment loss, so their results composed the first meta-analysis (Figure 2A). The studies were not heterogeneous (p=0.086), and the combined measure was a relative risk of 0.58 (95%CI: 0.29-1.12). The effect of periodontal treatment on PTB was not statistically significant.

For the second analysis, studies that controlled for multiparity were: Tarannum et al. 2007, Offenbacher et al. 2006, Michalowicz et al. 2006, López et al. 2002, Jeffcoat et al. 2003. Pooling the results of those studies, a second meta-analysis was conducted (Figure 2B). From the two studies excluded, one did not mention information about this confounder (45); the other (38) did not find significant difference between control and treatment groups for that variable,

with a p value=0.07, but did not do a multivariate analysis. In that second analysis, studies were not heterogeneous (p=0.080), and the combined relative risk was 0.77 (95%CI: 0.55-1.07), suggesting a non statistical association between periodontal treatment and PTB incidence.

Studies that have controlled for previous PTB were included in a third analysis. From the seven RCTs, five controlled for previous PTB: Radnai et al. 2009, Offenbacher et al. 2006, Michalowicz et al. 2006, Jeffcoat et al. 2003, López et al. 2002 and had their results pooled in a third meta-analysis (Figure 2C). From the two studies excluded, one did not mentioned controlling for that variable (41) and the other did not find significant difference between treatment and control groups for that variable, with a p value=0.1, but did not do a multivariate analysis (45). That third analysis showed non heterogeneity among studies (p=0.065) and a combined relative risk of 0.75(95% CI: 0.51-1.10). Again, the effect of periodontal treatment on PTB was not significant.

In the fourth analysis, from the seven initial studies, only one have not mentioned controlling for genitourinary infection (38), so the other six studies were included in the fourth meta-analysis (Figure 2D). The result for heterogeneity test was that studies were not heterogeneous (p=0.083) and the pooled relative risk was 0.75 (95% CI: 0.57-1.05). That shows a non significant effect of periodontal disease treatment on PTB.

When considering all of the above mentioned characteristics (probing depth and attachment loss measures and control for multiparity, previous PTB and infections) essential, there were only three remaining studies: Offenbacher et al. 2006, Michalowicz et al. 2006, López et al. 2002. In that sense, a fifth meta-analysis was done (Figure 3A). Studies were again not heterogeneous (p=0.078) and the combined relative risk was 0.63 (95% CI: 0.32-1.22), showing a non significant effect of periodontal treatment on PTB.

Since low birth weight was assessed only by the studies of Michalowicz et al. 2006 and López et al. 2002 and both studies were controlled for all of the four characteristics cited above, a sixth meta-analysis was conducted for LBW (Figure 3B). Both studies were not heterogeneous (p=0.102) and their results pooled generated a combined relative risk of 0.52 (95% CI: 0.10-2.60). There effect of periodontal therapy on LBW was not significant.

## Discussion

Clinical guidelines based on systematic reviews of RCTs consist of a link between scientific evidence obtained from empirical research and clinical practice in both medical and dental areas. They are extremely useful for decision makers in health, including health

professionals and administrators. Especially on subjects that there are non consensuses, such as the possible harmful effect of the periodontal disease on PTB and LBW occurrence, systematic reviews are essential. In addition, this need is reinforced because of the great number of interventional studies on this issue recently published.

As far as the authors are concerned, only one meta-analysis focused on the RCTs of the effect of periodontal disease treatment during pregnancy on PTB incidence was published (31). However, our results differed significantly from that recently meta-analysis published by Polyzos *et al* (31). The previous meta-analysis have obtained a pooled OR of 0.55 (95% CI, 0.35-0.86) for PTB, and OR of 0.48 (95% CI, 0.23-1.00) for LBW, suggesting that treatment with scaling and/or root planning during pregnancy significantly reduces the rate of PTB and may reduce the rate of LBW infants. On the other hand, all pooled RRs obtained in the current study were not statistically significant and potential explanations for such differences must be discussed. We argue that Polyzos *et al* (31) review is potentially flawed by methodological errors. The other meta-analysis included RCTs that used different periodontal disease diagnostic criteria. Some RCTs diagnosed periodontal disease using CAL as a unique criterion, others considered CAL and PPD and others included only gingivitis. Furthermore, the previous review obtained pooled estimatives from studies that did not control for confounders, including multiparity, previous preterm birth and other infections. The inclusion of potential biased studies may explain the discrepancies between our findings and the previous one. Results from RCTs produce the best evidence among all epidemiological studies. This is because of the randomization procedure, which is a technique used to assure that potential confounders are homogeneously distributed between groups. However, the effectiveness of randomization in RCTs must be confirmed by presenting evidence that the confounders were equally distributed between control and test groups. So, the lack of homogeneous distribution of the confounders, multiparity, previous PTB and genitourinary infection in some RCTs prompted us to conduct separated meta-analysis.

In our analysis we first excluded the RCT that evaluated the treatment of gingivitis (46). Then we performed 4 meta-analysis grouping studies according to periodontal disease diagnostic criteria and according to control for the following confounding variables: multiparity, previous PTB and genitourinary infection. There are other important risk factors for PTB and LBW, such as maternal age (<18 and >35 years old), lower socio-economic status, smoking, HIV infection, hypertension, diabetes, antibiotics use and multiple births. However, those factors were properly controlled by the selected RCTs. In all meta-analysis we performed periodontal treatment was not associated with lower incidence of PTB. A fifth analysis pooling

studies that attended the four criteria, again, did not show a protective effect of periodontal treatment on adverse pregnancy outcomes. LBW was assessed only by two studies and both attended all the four criteria and a sixth meta-analysis was conducted. Periodontal treatment did not significantly protected against LBW either.

In the present meta-analysis random effect methods were used. Although no heterogeneity was detected among the included studies, it was assumed that there were different underlying effect for each study and random effect methods takes this issue into consideration as an additional source of variation, which leads to somewhat wider confidence intervals than the fixed effects model. Random effects are assumed to be randomly distributed, and the central point of this distribution is the focus of the combined effect estimate (37).

In the present study the authors focused to answer the following question: Is there beneficial effect of periodontal treatment in the reduction of PTB and LBW incidence? Based on our findings, the answer for the raised question is no. Collected and adequately pooled data from studies published until now suggest that there is no evidence of a protective effect of periodontal therapy in reducing PTB and LBW. Treatment of periodontal disease cannot be recommended for pregnant women with the specific purpose of reducing adverse pregnancy outcomes. It is not possible yet to conclude that periodontal treatment has a protector effect against preterm birth and low birth weight.

Clearly, periodontal disease is an oral infection that must be always treated when diagnosed in order to promote oral health, but yet we cannot recommend it largely for pregnant women with the goal of reducing PTB and LBW.

**References**

1. World Health Organization, International statistical classification of diseases and related health problems. 10th Revision, 2007.
2. United Nations Children's Fund and World Health Organization, Low Birth weight: Country, regional and global estimates. UNICEF, New York, 2004.
3. Kliegman RM, Rottman CJ, Behrman RE. Strategies for the prevention of low birth weight. American Journal of Obstetrics and Gynecology 1990;162(4):1073-83.
4. Ohlsson A, Shah P. IHE Report. Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence. December, 2008.
5. Pollack RN, Divon MY. Intrauterine growth retardation: definition, classification, and etiology. Clinical Obstetrics and Gynecology 1992;35(1):99-107.
6. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2(8663):577-80.
7. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1(8489):1077-81.
8. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341(8850):938-41.

9. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663-737.
10. Vettore MV, Lamarca GA, Leão ATT, Thomaz FB, Sheiham A, Leal MC.Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies. Cad Saude Publica 2006;22(10): 2041-53.
11. Freitas F, Martins-Costa SH, Ramos JGL, Magalhães JA. Rotinas em Obstetrícia. 5ª. Edição, Porto Alegre: Artmed, 2006.
12. Gibbs RS, R Romero, SL Hillier, DA Eschenbach, RL Sweet: A review of premature birth and subclinical infection. Am J Obstet Gynecol 166 (1992) 1515.
13. Mazor M, W Chaim, S Horowitz, R Romero, M Glezerman: The biomolecular mechanisms of preterm labor in women with intrauterine infection. Isr J Med Sci 30 (1994) 317.
14. Lettieri L, AM Vintzileos, JF Rodis, SM Albini, CM Salafia: Does ‘‘idiopathic’’ preterm labor resulting in preterm birth exist? Am J Obstet Gynecol 1993; 168:1480.
15. Oliver R, RF Lamont: Role of cytokines in spontaneous preterm labour and preterm birth. In: Studd J: Progress in Obstetrics and Gynaecology. London, Churchill Livingstone 2004; 16:83–106.
16. Collins JG, Smith MA, Arnold RR, Offenbacher S. Effects of E.coli and P.gingivalis Lipopolysaccharide on pregnancy outcome in the golden hamster. Infecction and Immunity 1994a; 62:4652-5.
17. Collins JG, Windley HW, Arnold RR, Offenbacher S. Effects of a Porphyromonas gingivalis infection on inflammatory mediator response and pregnancy outcomes in hamsters. Infecction and Immunity 1994b; 62:4356-61.
18. Offenbacher S, HL Jared, PG O’Reilly, SR Wells, GE Salvi, HP Lawrence, et al.: Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontol 1998; 3:233.
19. Lopez NJ, PC Smith, J Gutierrez: Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol 2002; 73:911-924.
20. Oittinen J, T Kurki, M Kekki, M Kuusisto, P Pussinen, T Vilkuna-Rautiainen, et al.: Periodontal disease and bacterial vaginosis increase the risk for adverse pregnancy outcome. Infect Dis Obstet Gynecol 2005; 13:213.
21. Romero R, Wu YK, Mazor M, Hobbing JC, Mitchell MD. Amniotic fluid prostaglandin E2 in preterm labor. Prostaglandins Leukotrienes Essent. Fatty Acids 1988; 34:141-5.
22. Beutler B, Cerami A. The biology of cachectin/TNF-α. A primary mediator of the host response. Annu Rev Immunol 1989; 7:625-55.
23. Àgueda A, Echeverría A, Manau C. Association between periodontitis in pregnancy and preterm or low birth weight: Review of the literature. Med Oral Patol Oral Cir Bucal 2008; 13(9):E609-15.
24. Michalowicz BS, Durand R. Maternal periodontal disease and spontaneous preterm birth. Periodontol 2000;44(1):103-12.
25. Bobetsis YA, Barros SP, Offenbacher S. Exploring the relationship between periodontal disease and pregnancy complications. JADA 2006;137(10S):7S-13S.
26. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. J. Perinat. Med. 2007;35:93–9.
27. Silk H, Douglass AB, Douglass JM, Silk L. Oral Health During Pregnancy. HealthAm Fam Physician. 2008;77(8):1139-44.
28. Clothier B, Stringer M, Jeffcoat MK. Periodontal disease and pregnancy outcomes: exposure, risk and intervention. Best Pract Res Clin Obstet Gynaecol. 2007;21(3):451-466.
29. Vergnes J-N, Sixou M. Preterm low birth weight and maternal periodontal status: A meta analysis. Am J Obstet Gynecol 2007;196:135.e1-135.e7.

30. Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG 2006; 113:135–143.
31. Polyzos NP, MD; Polyzos IP, Mauri D, Tzioras S, Tsappi M, Cortinovis I, Casazza G. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a metaanalysis of randomized trials. Am J Obstet Gynecol 2009; 200(3):225-32.
32. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T. The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration. Ann Intern Med 2001;134:663-94.
33. Academy Report. Epidemiology of Periodontal Diseases – Position Paper. J Periodontol 2005;76:1406-19.
34. Maldonado G, Greenland S. Simulation Study of Confounder-Selection Strategies. Am J Epidemiol 1993;138(11): 923-36.
35. Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, Copper RL, Johnson F, Thom E, McNellis D, Miodovnik M, Menard MK, Caritis SN, Thurnau GR, Bottoms SF, Roberts J. The preterm prediction study: a clinical risk assessment system. Am J Obstet Gynecol 1996;174:1885–93; discussion 1893–1895.
36. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. Acta Obstet Gynecol Scand 2005;84:572–7.
37. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009.
38. Radnai M, Pál A, Novák T, Urbán E, Eller J, Gorzó I. Benefits of Periodontal Therapy When Preterm Birth Threatens 2009; J Dent Res 88(3):280-284.
39. Radnai M, Pál A, Novák T, Urbán E, Eller J, Heffter N, Horvath G. The possible effect of basic periodontal treatment on the outcome of pregnancy. Fogorv Sz 2008; 101(5):179-85.
40. Novak MJ, Novak KF, Hodges JS, Kirakodu S, Govindaswami M, DiAngelis A, Buchanan W, Papapanou PN, Michalowicz BS. Periodontal Bacterial Profiles in Pregnant Women: Response to Treatment and Associations With Birth Outcomes in the Obstetrics and Periodontal Therapy (OPT) Study. J Periodontol 2008;79:1870-1879.
41. Tarannum F, Faizuddin M. Effect of Periodontal Therapy on Pregnancy Outcome in Women Affected by Periodontitis. J Periodontol 2007;78:2095-2103.
42. Gazolla CM, Ribeiro A, Moysés MR, Oliveira LAM, Pereira LJ, Sallum AW. Evaluation of the Incidence of Preterm Low Birth Weight in Patients Undergoing Periodontal Therapy. J Periodontol 2007;78:842-848.
43. Offenbacher S, Lin D, Strauss R, McKaig R, Irving J, Barros SP, Moss K, Barrow DA, Hefti A, Beck JD. Effects of Periodontal Therapy During Pregnancy on Periodontal Status, Biologic Parameters, and Pregnancy Outcomes: A Pilot Study. J Periodontol 2006;77:2011-2024.
44. Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA. Treatment of Periodontal Disease and the Risk of Preterm Birth 2006; 355(18):1885-94.
45. Sadatmansouri SA, Sedighpoor NB, Aghaloo MC. Effects of periodontal treatment phase I on birth term and birth weight. J Indian Soc Pedod Prev Dent 2006; 24(1):23-6.
46. López 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;76:2144-53.
47. Jeffcoat MK, Hauth JC, Geurs NC, Reddy MS, Cliver SP, Hodgkins PM, Goldenberg RL. Periodontal disease and preterm birth: results of a pilot intervention study. J Periodontol 2003;74(8):1214-8.

## 5. CONCLUSÃO

A resposta para a pergunta inicialmente formulada – há efeito benéfico do tratamento periodontal na redução da incidência de parto prematuro e baixo peso ao nascer? – é não. As informações coletadas e adequadamente somadas dos estudos clínicos randomizados publicados até o momento sugerem que não há evidências de um efeito protetor do tratamento periodontal sobre os desfechos adversos da gravidez. O tratamento da doença periodontal não pode, portanto, ser recomendado a gestantes com a prerrogativa de reduzir tais desfechos.

**REFERÊNCIAS**

Academy Report. Epidemiology of Periodontal Diseases – Position Paper. J Periodontol 2005;76:1406-19.

Àgueda A, Echeverría A, Manau C. Association between periodontitis in pregnancy and preterm or low birth weight: Review of the literature. Med Oral Patol Oral Cir Bucal 2008; 13(9):E609-15.

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration. Ann Intern Med 2001;134:663-94.

Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341(8850):938-41.

Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1(8489):1077-81.

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2(8663):577-80.

Beutler B, Cerami A. The biology of cachectin/TNF-α. A primary mediator of the host response. Annu Rev Immunol 1989; 7:625-55.

Bobetsis YA, Barros SP, Offenbacher S. Exploring the relationship between periodontal disease and pregnancy complications. JADA 2006;137(10S):7S-13S.

Clothier B, Stringer M, Jeffcoat MK. Periodontal disease and pregnancy outcomes: exposure, risk and intervention. Best Pract Res Clin Obstet Gynaecol. 2007;21(3):451-466.

Collins JG, Smith MA, Arnold RR, Offenbacher S. Effects of E.coli and P.gingivalis Lipopolysaccharide on pregnancy outcome in the golden hamster. Infecction and Immunity 1994a; 62:4652-5.

Collins JG, Windley HW, Arnold RR, Offenbacher S. Effects of a Porphyromonas gingivalis infection on inflammatory mediator response and pregnancy outcomes in hamsters. Infecction and Immunity 1994b; 62:4356-61.

Freitas F, Martins-Costa SH, Ramos JGL, Magalhães JA. Rotinas em obstetrícia. 5ª edição; Porto Alegre: Artmed, 2006.

Gazolla CM, Ribeiro A, Moysés MR, Oliveira LAM, Pereira LJ, Sallum AW. Evaluation of the Incidence of Preterm Low Birth Weight in Patients Undergoing Periodontal Therapy. J Periodontol 2007;78:842-848.

Gibbs RS, R Romero, SL Hillier, DA Eschenbach, RL Sweet: A review of premature birth and subclinical infection. Am J Obstet Gynecol 1992;166:1515.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009.

Jeffcoat MK, Hauth JC, Geurs NC, Reddy MS, Cliver SP, Hodgkins PM, Goldenberg RL. Periodontal disease and preterm birth: results of a pilot intervention study. J Periodontol 2003;74(8):1214-8.

Kliegman RM, Rottman CJ, Behrman RE. Strategies for the prevention of low birth weight. American Journal of Obstetrics and Gynecology 1990;162(4):1073-83.

Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663-737.

Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. Acta Obstet Gynecol Scand 2005;84:572–7.

Lettieri L, AM Vintzileos, JF Rodis, SM Albini, CM Salafia: Does ‘‘idiopathic’’ preterm labor resulting in preterm birth exist? Am J Obstet Gynecol 1993; 168:1480.

López 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;76:2144-53.

López NJ, PC Smith, J Gutierrez: Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol 2002; 73:911.

Maldonado G, Greenland S. Simulation Study of Confounder-Selection Strategies. Am J Epidemiol 1993;138(11): 923-36.

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;35:385–397.

Mazor M, W Chaim, S Horowitz, R Romero, M Glezerman: The biomolecular mechanisms of preterm labor in women with intrauterine infection. Isr J Med Sci 1994;30:317.

Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, Copper RL, Johnson F, Thom E, McNellis D, Miodovnik M, Menard MK, Caritis SN, Thurnau GR, Bottoms SF, Roberts J. The preterm prediction study: a clinical risk assessment system. Am J Obstet Gynecol 1996;174:1885–93; discussion 1893–1895.

Michalowicz BS, Durand R. Maternal periodontal disease and spontaneous preterm birth. Periodontol 2000 2007;44(1):103-12.

Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA. Treatment of Periodontal Disease and the Risk of Preterm Birth 2006; 355(18):1885-94.

Novak MJ, Novak KF, Hodges JS, Kirakodu S, Govindaswami M, DiAngelis A, Buchanan W, Papapanou PN, Michalowicz BS. Periodontal Bacterial Profiles in Pregnant Women: Response to Treatment and Associations With Birth Outcomes in the Obstetrics and Periodontal Therapy (OPT) Study. J Periodontol 2008;79:1870-1879.

Offenbacher S, HL Jared, PG O'Reilly, SR Wells, GE Salvi, HP Lawrence, et al.: Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontol 1998; 3:233.

Offenbacher S, Lin D, Strauss R, McKaig R, Irving J, Barros SP, Moss K, Barrow DA, Hefti A, Beck JD. Effects of Periodontal Therapy During Pregnancy on Periodontal Status, Biologic Parameters, and Pregnancy Outcomes: A Pilot Study. J Periodontol 2006;77:2011-2024.

Ohlsson A, Shah P. IHE Report. Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence. December, 2008.

Oittinen J, T Kurki, M Kekki, M Kuusisto, P Pussinen, T Vilkuna-Rautiainen, et al.: Periodontal disease and bacterial vaginosis increase the risk for adverse pregnancy outcome. Infect Dis Obstet Gynecol 2005; 13:213.

Oliver R, RF Lamont: Role of cytokines in spontaneous preterm labour and preterm birth. In: Studd J: Progress in Obstetrics and Gynaecology. London, Churchill Livingstone 2004; 16:83–106.

Petrou S. Economic consequences of preterm birth and low birthweight. BJOG: an International Journal of Obstetrics and Gynaecology 2003;110(Suppl 20):17-23.

Pollack RN, Divon MY. Intrauterine growth retardation: definition, classification, and etiology. Clinical Obstetrics and Gynecology 1992;35(1):99-107.

Polyzos NP, MD; Polyzos IP, Mauri D, Tzioras S, Tsappi M, Cortinovis I, Casazza G. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a metaanalysis of randomized trials. Am J Obstet Gynecol 2009; 200(3):225-32.

Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. J. Perinat. Med. 2007;35:93–9.

Radnai M, Pál A, Novák T, Urbán E, Eller J, Gorzó I. Benefits of Periodontal Therapy When Preterm Birth Threatens 2009; J Dent Res 88(3):280-284.

Radnai M, Pál A, Novák T, Urbán E, Eller J, Heffter N, Horvath G. The possible effect of basic periodontal treatment on the outcome of pregnancy. Fogorv Sz 2008; 101(5):179-85.

Romero R, Wu YK, Mazor M, Hobbing JC, Mitchell MD. Amniotic fluid prostaglandin E2 in preterm labor. Prostaglandins Leukotrienes Essent. Fatty Acids 1988; 34:141-5.

Sadatmansouri SA, Sedighpoor NB, Aghaloo MC. Effects of periodontal treatment phase I on birth term and birth weight. J Indian Soc Pedod Prev Dent 2006; 24(1):23-6.

Silk H, Douglass AB, Douglass JM, Silk L. Oral Health During Pregnancy. HealthAm Fam Physician. 2008;77(8):1139-44.

Tarannum F, Faizuddin M. Effect of Periodontal Therapy on Pregnancy Outcome in Women Affected by Periodontitis. J Periodontol 2007;78:2095-2103.

United Nations Children's Fund and World Health Organization, Low Birth weight: Country, regional and global estimates. UNICEF, New York, 2004.

Vergnes J-N, Sixou M. Preterm low birth weight and maternal periodontal status: A meta analysis. Am J Obstet Gynecol 2007;196:135.e1-135.e7.

Vettore MV, Lamarca GA, Leão ATT, Thomaz FB, Sheiham A, Leal MC. Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies. Cad Saude Publica 2006;22(10): 2041-53.

World Health Organization, International statistical classification of diseases and related health problems. 10th Revision, 2007.

Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG 2006; 113:135–143.

**ANEXOS**

**Table 1** - Evaluation of studies according to main items of CONSORT *(Unclear: papers without the respective information; PD: probing depth; BOP: bleeding on probing; AL: attachment loss).*

| Paper Section | Title and Abstract | Introduction | Methods | | | | |
|---|---|---|---|---|---|---|---|
| Articles / Topic | Title and Abstract | Justify need for a new trial | Inclusion Criteria | Exclusion Criteria | Settings and locations | Ramdomization | Blinding |
| Radnai et al. 2009 | Title: No Abstract:No | Adequate | Women with periodontal disease | Any systemic problem, multiple pregnancy, history of previous pre-term birth or miscarriage, mothers who smoked, consumed alcoholic drinks in a great amount, took drugs, suffered malnutrition, who would require antibiotics for invasive procedures. | Department of Obstetrics & Gynecology in Szeged | Yes | Adequate |
| Tarannum et al. 2007 | Title: No Abstract:Yes | Unclear | Healthy women, aged 18 to 35 years; single gestation between 9 and 21 weeks | Use of tobacco or alcohol; congenital heart disease; use of corticosteroids; diabetes, asthma, glomerulonephritis, or hyperthyroidism; twin pregnancies and Rh factor isoimmunity; current antibiotic treatment; and clinically evident systemic infection | Department of Obstetrics and Gynecology, Dr. B.R. Ambedkar Medical College and Hospital, Bangalore, Karnataka, India | Yes | Unclear |
| Offenbacher et al. 2006 | Title: No Abstract: Yes | Adequate | Pregnant women, <22 weeks gestation; prior PTLBW delivery; ≥18 years old | Multiple births, HIV infection, AIDS, diabetes (gestational diabetes was acceptable), medical contraindication to periodontal probing, use of phentermine and fenfluramine (phen-fen) for weight loss; undergoing periodontal treatment; chronic regimen of aspirin or non-steroidal anti-inflammatory drug; use of medications that cause gingival enlargement; five or more teeth requiring extraction; rampant decay or any other oral condition that, in the clinician's judgment,would place the patient at unacceptable risk if treatment was delayed; using chlorhexidine or other mouthrinses | WakeCounty,NorthCarolina HumanServicesprenatal clinic and the Wake County Area Health Education Center (AHEC) high-risk prenatal clinic at WakeMed Hospital, Raleigh, North Carolina | Yes | Unclear |
| Michalowicz et al. 2006 | Title: No Abstract: Yes | Adequate | At least 20 natural teeth and the presence of periodontal disease | Multiple fetuses, antibiotic prophylaxis for periodontal procedures, medical condition that precluded elective dental treatment, extensive tooth decay, fewer than 20 teeth after initial treatment | Hennepin County Medical Center, the University of Kentucky, the University of Mississippi Medical Center, and Harlem Hospital | Yes | Adequate |
| Sadatmansouri et al. 2006 | Title: No Abstract: Yes | Adequate | Women: 18 to 35 year age, with moderate or advanced periodontal disease, in the 13th to 20th week of pregnancy | History of congenital heart disease requiring prophylactic antibiotics, diabetes, use of corticosteroids, chronic renal disease, fetal congenital abnormality (evaluated ultrasonically until the 20th week) | Javaheri hospital | Yes | Unclear |
| Jeffcoat et al. 2003 | Title: No Abstract: Yes | Adequate | Women between 21 and 25 weeks' gestation with periodontal disease | Women participating in any other treatment study, patients undergoing periodontal therapy, taking antibiotics during pregnancy, using antimicrobials mouthrinses, patients requiring treatment for bacterial vaginosis | University of Alabama at Birmingham Shool of Dentistry | Yes | Adequate |
| López et al. 2002 | Title: Yes Abstract:Yes | Adequate | Healthy women, aged 18 to 35, with a singleton gestation, between 9 and 21 weeks of gestation, with periodontal disease | History of congenital heart disease requiring prophylactic antibiotics, existing diabetes before pregnancy, current use of corticosteroids, chronic renal disease, intention to deliver at a hospital other than that of the study | Consultorio Carol Urzúa of Peñalolén, Santiago, Chile | Yes | Adequate |

| Results | | | | | Discussion | | | |
|---|---|---|---|---|---|---|---|---|
| Flow of participants | Recruitment | Follow-up | Numbers Analyzed | Outcomes and Estimation | Limitations | Generalizability | Diagnoses of Periodontal Disease | Calibration |
| Adequate | 2005 and 2006 | Unclear | Treatment group: 41; Control group: 42 | Adequate | Unclear | Unclear | ≥ 4 mm PD, at least at one site, and BOP for ≥ 50% of teeth. | Adequate |
| Adequate | August 2004 - August 2005 | Regular checkups 3-5 weeks interval | Control group: 89; Treatment group: 91. Intention-to-treat and per protocol analyses were done. | Inadequate | Classification of socioeconomic status was based only on occupation; the exclusion of subjects with systemic infections was based on clinical presentation; hence, subjects with subclinical infection must have been included; subjects with a history of alcohol/tobacco use were excluded from the study; the results of the study do not apply to the entire Indian population. | Adequate | ≥20 completely erupted teeth, excluding the third molars; and subjects with ≥2 mm AL at ≥50% of examined sites | Unclear |
| Adequate | January 2001 - November 2003 | Regular checkups 4-6 weeks interval | 35 subjects in the intervention group and 32 control subjects | Adequate | Single-centered, included small numbers of subjects, the study was not powered to detect statistical differences between groups | Adequate | two or more sites measuring ≥5 mm PD + AL of 1 to 2 mm at one or more sites with PDs ≥5 mm; | Adequate |
| Adequate | March 2003 - June 2005 | Periodontal treatment before 21 weeks; Regular checkups: six follow-up visits | Treatment group: 413; control group: 410. All analyses on an intention-to-treat basis unless stated otherwise | Adequate | It is possible that periodontal therapy was delivered too late in pregnancy to affect birth outcomes | Unclear | 4 or more teeth with a PD of at least 4 mm and a AL of at least 2 mm, BOP at 35% or more of tooth sites | Adequate |
| Unclear | 2004-2005 | Periodontal evaluation once every two weeks prior to delivery | Treatment group: 15; control group: 15 | Inadequate | Unclear | Unclear | 4 or more than 4 teeth, with at least one site with PD of (equal or more than 4 mm) and AL of (equal or more than 3 mm) | Unclear |
| Adequate | Unclear | Unclear | Control group: 123, Treatment group: 123, Treatment + metronidazole group: 120 Intention-to-treat analyse was done. | Adequate | The results cannot be generalized to pregnant women at large; the results are in no way applicable to pregnant women without periodontal disease | Adequate | At least 3 sites with AL ≥3 mm | Unclear |
| Adequate | Over a 20-month period | Periodontal therapy: completed before 28 weeks of gestation; Maintenance therapy: every 2 to 3 weeks until delivery | Treatment group: 163, Control group: 188. Intention-to-treat and per protocol analyses were done. | Adequate | Unclear | Unclear | 4 or more teeth with 1 or more sites with PD≥4 mm and with AL≥3 mm at the same site | Adequate |

**Table 2** - Therapies applied to intervention, control and maintenance groups by studies analyzed *(SRP: scaling and root planning; Prophy: prophylaxis; √: OK; X: not done; Unclear: maintenance was performed but the procedures were not mentioned).*

| | Intervention Group | | | | | Control Group | | | Maintenance | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plaque Control Instruct. | Prophy | Supragingival Scaling | SRP | 0.12% chlorhexidine mouthrinse twice daily | Plaque Control Instruct. | Prophy | Supragingival Scaling | Plaque Control Instruct. | Prophy | Supragingival Debridement |
| Radnai et al. 2009 | √ | √ | √ | √ | X | X | X | X | Not mentioned | | |
| Tarannum et al. 2007 | √ | X | √ | √ | √ | √ | X | X | √ | √ | X |
| Offenbacher et al. 2006 | √ | √ | √ | √ | X | √ | X | √ | Not mentioned | | |
| Michalowicz et al. 2006 | √ | X | √ | √ | X | X | X | X | √ | √ | √ |
| Sadatmansouri et al. 2006 | √ | X | √ | √ | √ | X | X | X | √ | X | X |
| Jeffcoat et al. 2003 | √ | X | √ | √ | X | √ | √ | √ | Not mentioned | | |
| López et al. 2002 | √ | X | √ | √ | √ | X | X | X | Unclear | | |

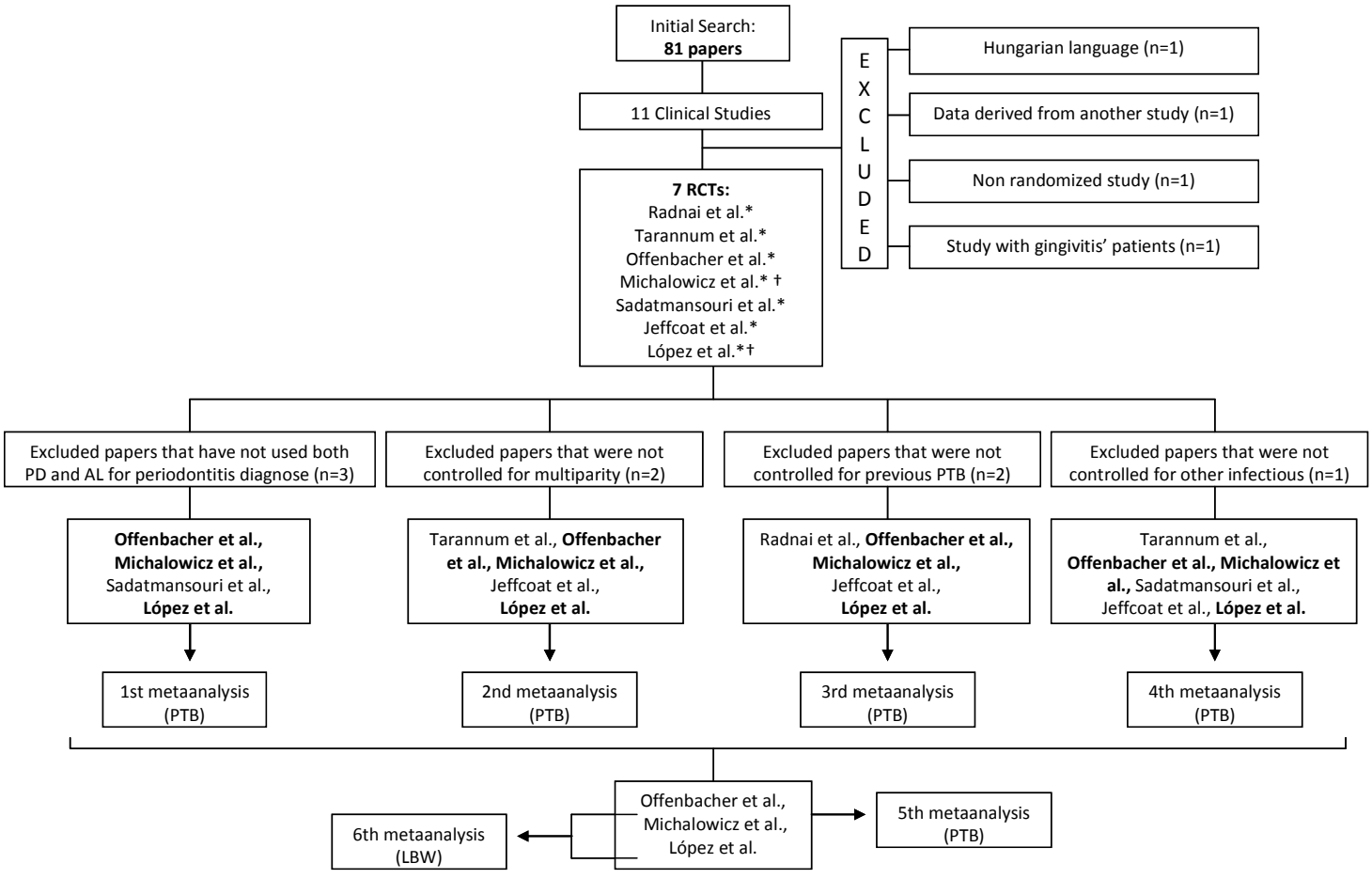


**Figure 1**- Flow chart of the studies included by different criteria and meta-analyses performed *(* Preterm birth- PTB; † Low birth weight-LBW).*

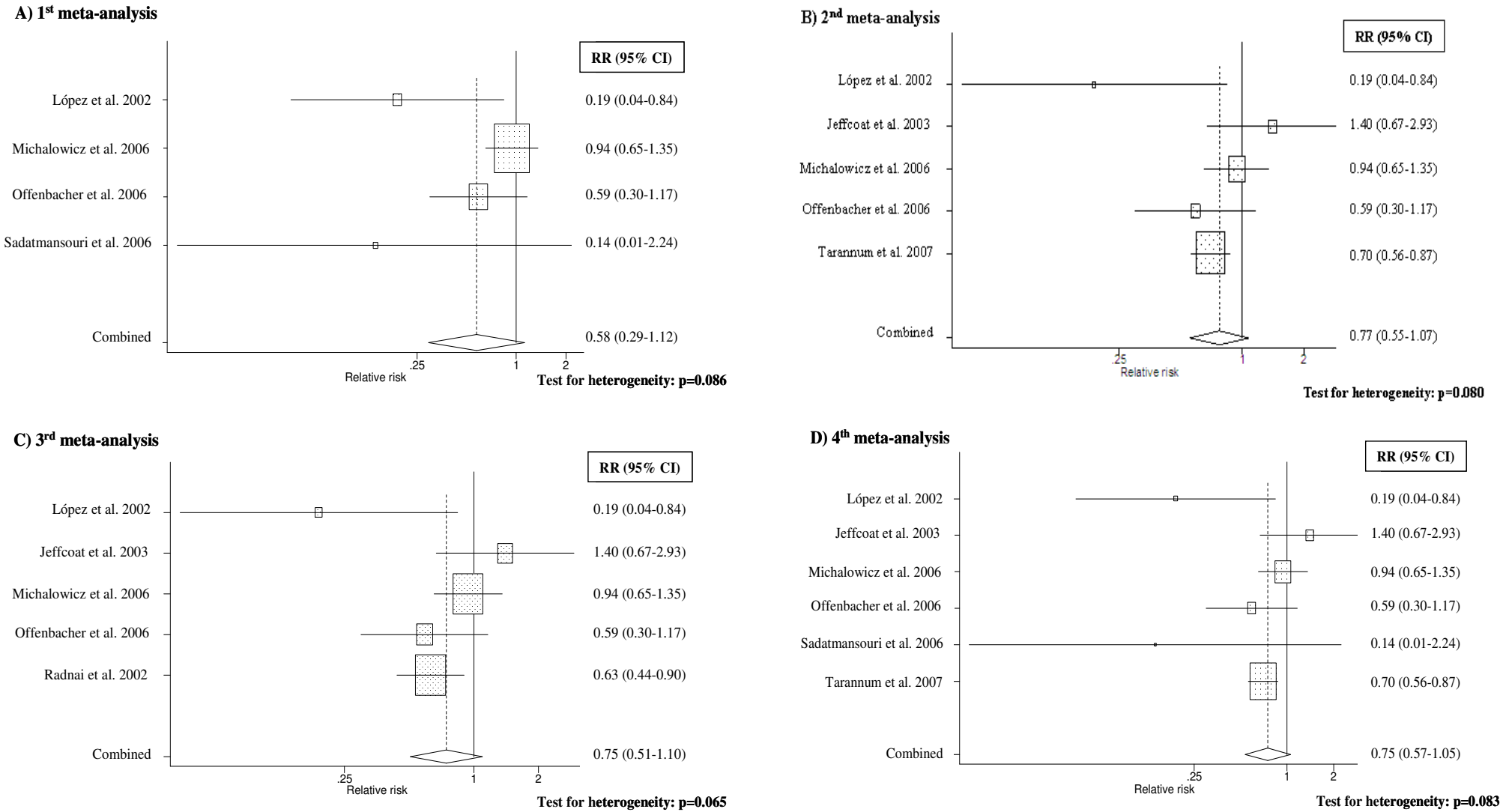


**Figure 2** - Meta-analysis performed for the four different criteria initially applied to the RCTs considering outcome PTB. **A)** First meta-analyses with studies that used both PD and AL; **B)** Second meta-analyses with studies controlling for multiparity; **C)** Third meta-analyses with studies that have controlled for previous PTB; **D)** Fourth meta-analyses with studies controlling for genitourinary infections *(RR: relative risk; CI: confidence interval; p: P value).*

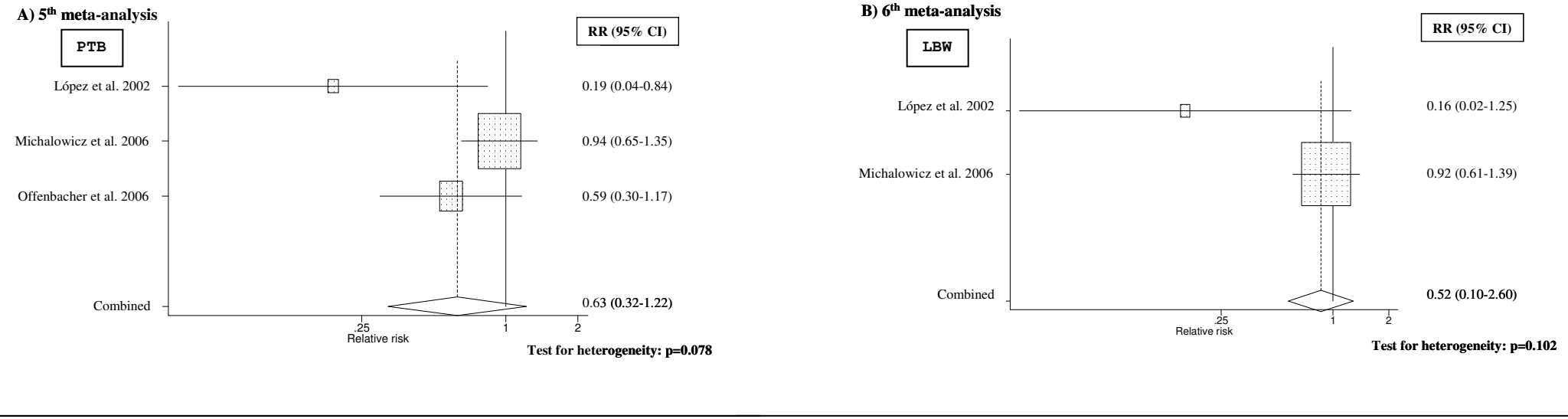


**Figure 3** - Meta-analyses performed for the studies that combined all the four mentioned characteristics (probing depth and attachment level measures and control for multiparity, previous PTB and infections). **A)** Fifth meta-analysis for PTB; **B)** Sixth meta-analysis for LBW *(RR: relative risk; CI: confidence interval; p: P value).*

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