

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Low birth weight is a leading perinatal problem world-wide, and may account for a sizable percentage of perinatal morbidity and mortality.¹ The World Health Organization (WHO) defines the condition as a baby born with a birth weight lower than 2.5 kg, due to either a short gestational period or to intrauterine growth delay.¹ Low birth weight is not synonymous with preterm deliveries. Low birth weight refers to infants weighing less than 2.5 kg, whereas preterm infants are infants born before 37 weeks of pregnancy have been completed. Thus, a low birth weight infant could be born preterm or could be born at a normal gestation period following a period of poor intrauterine fetal growth.

Babies with low birth weight look much smaller than babies of normal birth weight. A low birth weight baby's head may appear to be bigger than the rest of the body and the baby often looks thin, with little body fat (see Figure 1, overleaf).

Compared to normal weight newborns, babies with this condition face a higher risk of serious health problems, lasting disabilities and even death during the neonatal period.² Medical problems that are common in low birth weight babies include respiratory distress syndrome (RDS), intravascular haemorrhage (IVH),

patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP).³ They also demonstrate more behavioural abnormalities as preschoolers.³



Figure 1: A low birth weight baby

Factors that may contribute to fetal growth restriction include the following:³

- chronic health problems in the mother;
- smoking by the mother (active and passive);
- alcohol and illicit drug use by the mother;
- infections in the mother, particularly of the genitourinary tract;
- infections in the uterus;
- placenta problems such as abnormal placenta;
- inadequate maternal weight gain; and
- socio-economic factors such as unfavourable socio-economic conditions.

Low birth weight presents any community with several challenges. Increased susceptibility to infections and a range of medical complications, together with the added infrastructural, financial and human resources required to reduce mortality in such newborns, have generated interest in this condition in recent times.³

The low birth weight incidence rate has been used as an indicator for the socio-economic and general health status of women and the community at large.³ The South African low birth weight rate is on a par with the global rate of 15%.³ However, a much lower incidence of 4% in Sweden, 6% in Switzerland, and 8% in the United Kingdom³ illustrates the need for improvement, especially in the upstream factors required to decrease low birth weight rates in South Africa. The difference between low birth weight incidence rates in these developed countries and South Africa may be a reflection of the lower socio-economic and general health status of women and the larger community in South Africa compared to that of women in such developed countries.

Several scientific reports have implicated various factors as predisposing mothers to delivering low birth weight babies. However, medical professionals remain unable to predict the occurrence of low birth weight with absolute certainty and medical interventions are still unable to prevent this condition in many cases. This has led many health workers to hypothesize the presence of some as yet unidentified contributing factors, including periodontal disease during pregnancy⁴⁻⁵ that may be linked to an increased risk of low birth weight.

Periodontal disease (see Figure 2, overleaf) is an oral disease characterized by a Gram-negative bacterial infection that progresses from affecting the gingival

tissue to reaching the tooth-supporting structure. Although periodontal disease starts as a localized inflammatory condition in the oral cavity, it may present a risk factor for health problems and an inflammatory challenge at a systemic level.⁵ In the dental literature, periodontal diseases are generally classified into two groups, namely gingivitis (inflammation of the gingivae/gums) and periodontitis (a more severe inflammatory condition that progressively damages the tissues that support the teeth beneath the gum).⁵



Figure 2: Periodontal disease

Periodontal diseases are considered one of the most widespread diseases amongst humans. They are caused by the activity of bacteria that are present in dental plaque and that accumulate as a result of inadequate oral hygiene practices. Recently, the impact of periodontal disease in terms of adverse pregnancy outcomes, especially low birth weight, has received considerable attention.^{4,5} Since 1996, a number of studies have investigated the potential relationship between periodontal disease and low birth weight.^{6,7} The initial

results have been inconsistent,⁸ but more scientific evidence is beginning to emerge in support of a positive association between periodontal disease in pregnancy and the occurrence of low birth weight in new-borns.⁹ Most of the studies on this subject have been conducted in high-income countries, so that only limited information is available on the association between periodontal disease and low birth weight in low-income and middle-income countries, where both poor oral health and adverse reproductive outcomes are more prevalent.⁴

In South Africa, the prevalence of periodontal disease is high.¹⁰ Fewer than 2% of younger adults (between 35 and 44 years)¹⁰ and children younger than 15 years¹¹ in South Africa have healthy gums. Experiencing 'bleeding gum' when brushing the teeth gently and painful gums are the most common symptoms of periodontal diseases.¹² Periodontal disease is also an infectious disease, affecting more than 23% of women between the ages of 30 and 54 years.¹³

Once diagnosed, most periodontal diseases can be treated successfully. The therapeutic goals in periodontal therapy are threefold. The first aim is to alter or eliminate the origin of the microbes, as well as contributing risk factors, thereby preventing the progression of the disease and preserving the healthy state of the periodontium. The second goal is to prevent the recurrence of periodontal disease. Finally, in severe cases, regeneration of the periodontal attachments must be attempted.¹⁴

The paucity of studies from developing countries warrants more studies from this part of the world so that associations between low birth weight and periodontal disease can be considered from a developing country perspective. It is this gap that the current study attempts to address.

1.2 LITERATURE REVIEW

Periodontal disease is recognized as the second most prevalent oral disease after dental caries.¹⁵ It represents an important individual and public health problem, not only because of its relatively high prevalence, but also because of the way in which its effects go beyond the oral region.

The bacteria that form plaque also release toxins that stimulate the immune system to overproduce a powerful infection-fighting factor called cytokines. Ordinarily, cytokines, which are a hormone-like protein, are important for healing. In excess, however, they cause inflammation and tissue damage.¹⁵ Two cytokines that are important in periodontal disease are known as tumour necrotic factor-alpha (TNF-alpha) and interleukin-1 beta.¹⁵ In addition, white blood cells produced by the immune response to these bacteria also release a family of enzymes called matrix metalloproteinases (MMPs) which break down connective tissue. The integrity of the periodontium is thus broken by the activity of bacteria present in dental plaque.

Periodontal integrity can be maintained by means of the combined effects of host factors, adequate nutrition, adequate oral self-care and the absence of undermining systemic conditions.¹⁵ Factors such as smoking, alcohol intake, poor nutrition, and immune-suppression associated with diseases (such as diabetes or HIV) have also been known to pose a risk for periodontal disease.¹⁶

Evidence has accumulated to indicate that there is a relationship between periodontal disease and low birth weight.^{4-5,8} Other systemic conditions that have been associated with periodontal diseases include cardiovascular disease,

diabetes mellitus and osteoporosis.⁹ In addition to the biological components that contribute to the association between periodontal disease and low birth weight, there are a number of, other factors that are also relevant to the causal process of this association, such as unfavourable socio-economic conditions, difficulty in accessing health services and lifestyle habits that have a bearing on health, such as smoking and alcohol use.⁸

The ability of periodontal pathogens and their virulence factors to disseminate and induce both local and systemic inflammatory responses in the host has led to the hypothesis that periodontal disease may have consequences beyond the periodontal tissues themselves. Interestingly, this concept was reported by Miller¹⁶ as early as 1891, when he published the theory of ‘focal infection’. On the basis of this theory, oral foci of infection are considered responsible for a number of local and systemic diseases such as tonsillitis, pneumonia, endocarditis and septicaemia. However, because of a lack of scientific evidence, this theory was largely ignored, although Galloway¹⁸ suggested in 1931 that periodontal disease has more than just an association with, and can actually contribute to a low birth weight. It was only in the early 1990s, about a 100 years after Miller made his proposition, that Colin and colleagues¹⁷ hypothesized that an oral infection such as periodontitis could act as a source of bacteria and could be an inflammatory mediator that could disseminate systemically to the fetal-placental unit, via blood circulation, and induce complications in pregnancy.

In a series of landmark animal studies, Colin et al.¹⁷ demonstrated that in a hamster chamber model, chronic exposure to *Porphyromonas gingivalis* led to a

15% to 18% decrease in fetal weight, along with a local increase in prostaglandin E₂ (PGE₂) and tumour necrotic factors (TNFs) within the chamber fluid. Later they studied the association between infection and pregnancy by including periodontal disease in the hamster model. Four groups of animals were fed either control chow or plaque-promoting chow for an eight-week period to induce experimental periodontitis prior to mating. Two additional groups received exogenous *Porphyromonas gingivalis* via oral lavage. On the day of sacrifice, animals receiving both plaque-promoting chow and exogenous *Porphyromonas gingivalis* challenge demonstrated a significant 22.5% reduction in the mean fetal weight. These animal studies provided vital proof-of-principle experiments and suggested the possibility that low grade infections may indeed trigger maternal-fetal inflammation, resulting in adverse pregnancy events.

Periodontal disease is a Gram-negative infection and it may indeed have the potential to influence the outcome of a pregnancy. During pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases compared to the proportion of aerobic bacteria.¹⁹ In a study conducted by Li et al.,²⁰ *Fusobacterium nucleatum* and other subspecies emanating from the oral flora were found in the amniotic fluid of women with low birth weight. Evidence of an increased rate of amniotic fluid infections, chorioamnion infection and chorioamnionitis support an association between low birth weight and infection during pregnancy.²⁰ Histologically, the chorioamnion is often inflamed, even in the absence of any bacterial infection in the vagina or cervical area. This suggests that distant sites of infection or sepsis may be targeting the placenta membranes. Some case-control studies²⁰⁻²¹ have demonstrated that women who have low birth weight infants as a consequence of either preterm labour or

premature rupture of membranes tend to have more severe periodontal disease than mothers with normal birth weight infants.

Another study conducted by Bostrom et al.²² found that the Gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that may affect the host directly. It was suggested in their study that the microbial component, lipopolysaccharides, can activate the macrophages and other cells to synthesize and secrete a wide spectrum of molecules, including cytokines IL, TNFs, PGE₂ and MMPs. It was further suggested that if these components travel via the bloodstream and cross the placental barrier, the physiological levels of PGE₂ and TNFs in the amniotic fluid may increase and induce a pre-term birth, resulting in low birth weight.²²

In 2008, Marakoglu et al.²³ conducted a cross-sectional unmatched case-control study in Turkey. The aim of their study was to evaluate periodontal disease as a risk factor for low birth weight. The results indicated that periodontal disease was independent risk factor for low birth weight.

In 1996, Offenbacher et al.²⁴ conducted a case-control study in which they hypothesized that periodontal infection may be associated with low births. A case-control study of 124 pregnant or postpartum mothers was conducted, using mothers with normal birth weight babies as controls. The assessment included a broad range of known obstetric risk factors, such as tobacco and drug use, alcohol consumption, the level of prenatal care, parity, genitourinary infections and nutrition. Each subject received a periodontal examination to determine her clinical attachment level. Mothers of low birth weight infants and primiparous mothers of low birth infants had significantly worse periodontal

disease than the mothers of the normal birth weight infants. Multivariate logistic regression models used to control for other risk factors and covariates demonstrated that periodontal disease was a statistically significant risk factor for low birth weight, with adjusted odds ratios of 7.9 and 7.5 for all low birth weight cases and primiparous low birth weight cases respectively. These observations indicate that periodontal disease represents a previously unrecognized and clinically significant risk factor for low birth weight as a consequence of either preterm labour or premature rupture of the membrane.

Offenbacher et al.²⁵ also conducted a more recent case-control study, in which the gingival crevicular fluid (GCF) levels of PGE₂ and interleukin of 48 case-control subjects were measured to determine whether mediator levels are related to current pregnancy outcomes. In addition, the levels of four periodontal pathogens were measured by using microbe-specific DNA probes. The results indicated that the GCF PGE₂ levels were significantly higher in mothers of low birth weight infants than in mothers of normal birth weight infants (the control). Furthermore, among the primiparous mothers of pre-term low birth weight infants, there is a significant inverse association between birth weight and the GCF PGE₂ level. This study also suggested a dose-response relationship for increased GCF PGE₂ as a marker of current periodontal disease activity and decreasing birth weight. Four organisms associated with mature plaque and progressing periodontitis, namely *Acteroides forsythus*, *Porphyomonas gingivalis*, *Acteroides actinomycetemcomitans* and *Treponema denticola*, were detected and displayed higher levels in the mothers of pre-term low birth weight infants in the study than in the mothers in the control. These observations, taken together, suggest that biochemical measures of maternal periodontal status and an

elevated oral microbial burden are associated with preterm birth and low birth weight. Offenbacher et al.²⁵ concluded that 18.2% of the incidence of preterm low birth weight may result from periodontal disease.

Jeffcoat et al.²⁶ conducted a prospective cohort study among women between the ages of 20 and 30 years; 83% of the subjects were African Americans and the remaining 17% were Caucasians. Their study reported that maternal periodontal disease represents a significant risk factor for low birth weight. The adjusted prevalence of moderate to severe periodontal disease increased with reducing gestational age. It was concluded that the average newborn's weight and gestational age was inversely proportional to maternal periodontitis status. Xiong et al.²⁷ report that it has already been proven that periodontal disease is a major inflammatory precursor to adverse pregnancy outcomes and may be implicated in up to 50% of cases.

In 2002, Madianos et al.²⁸ analysed three studies published on the association between periodontal disease and an increased risk of coronary heart disease and preterm and/or low birth weight deliveries. Two out of the three eligible studies found a significant association between periodontitis and adverse pregnancy outcomes. The third study did not find any association. A study by Moreu et al.²⁹ also reports inconsistent results, concluding that periodontal disease was a significant risk factor for low birth weight, but not for pre-term delivery. Recently, in 2010, Rajn et al.³⁰ concluded that periodontal disease appears to be an independent risk factor for preterm low birth weight and that there is a need to expand preventive measures for pregnant women in

harmonization with the gynaecological and dental profession, and to provide professional oral hygiene measurement during pregnancy.

Since the pioneering study in 1996 by Offenbacher et al.²⁴ there has been increased interest in identifying the potential association between periodontal disease and pregnancy outcomes. Some intervention studies³¹⁻⁴⁰ have shown that providing periodontal treatment to pregnant women with periodontal disease improved pregnancy outcomes, buttressing the link between periodontal disease and adverse pregnancy outcomes.

Mitchell-Lewis et al.³² investigated the relationship between periodontal infections and low birth weight in a cohort of young, minority, pregnant and post-partum women. Periodontal treatment was provided to 74 pregnant women and the incidence of low birth weight was compared to that among 90 women studied after the birth of their babies. Although the incidence of adverse pregnancy outcomes was higher in women who had received no periodontal treatment, this difference was not statistically significant, due to the small sample size. However, the study did show that low birth weight mothers had significant levels of *Tannerella forsythensis* and *Campylobacter rectus*.³² Similarly, Lopez et al.³³ found a reduction in the rate of preterm births and/or low birth weight in women who received periodontal treatment before the 28th gestational week, compared to the rate among women who had not received any such treatment. This reduction was significant for women with both gingivitis and periodontal disease.³³⁻³⁵

Jeffcoat et al.³⁶ did a pilot study in which they enrolled 366 women with periodontitis between the 21st and 25th gestation weeks in three intervention

groups. In Group 1, the intervention consisted of dental prophylaxis plus a placebo capsule; in Group 2, it consisted of scaling and root planing plus a placebo capsule; and in Group 3, it consisted of scaling and root planing plus a metronidazole capsule. The researchers concluded that performing scaling and root planing in pregnant women with periodontitis may reduce low birth weight in that population, but that adjunctive metronidazole therapy did not improve pregnancy outcomes.

In 2009, Sha et al.³⁷ conducted a study in China which found that oral health instruction and periodontal treatment may decrease infection by periodontal pathogens and reduce the risk of low birth weight. They concluded that the best advice for a woman who is contemplating pregnancy is effective brushing two times per day and regular periodontal treatment. In Brazil, in a study to evaluate whether periodontal therapy among pregnant women would reduce the incidence of low birth weight, Cruz et al.³⁸ demonstrated that the frequency of low birth weight among women who had periodontal disease but who were treated was 9.22%, while it was 13.10% in the group without treatment for periodontal disease. This suggests that periodontal therapy is a protective factor against low birth weight.³⁸ In 2011, Sant'Ana et al.³⁹ also reported on another study conducted in Brazil which showed that performing periodontal treatment during the second trimester of gestation would decrease the risk that adverse pregnancy outcomes would develop. Their finding could imply that periodontal disease can be considered a risk factor for adverse pregnancy outcomes, especially preterm birth and/or low birth weight.

In a 1:1 matched case-control study (55 pairs), Dasanayake⁴⁰ tested the hypothesis that poor oral health in a pregnant woman is a risk factor for low birth weight. The effect of the periodontal and dental caries status of each mother on the birth weight of her infant was evaluated at the time of delivery by conditional logistic regression analysis, while controlling for known risk factors for low birth weight. Mothers of low birth weight infants were shorter, were less educated, and were married to men of lower occupational class, had fewer areas of healthy gingiva and more areas with bleeding and calculus (tartar), and gained less weight during pregnancy. Conditional logistic regression analysis indicated that mothers with more healthy gingival areas (odds ratio [OR] =0.3, 95% confidence interval [CI]=0.12 to 0.72) and those who were taller (OR=0.86, 95% CI=0.75 to 0.98) have a lower risk of giving birth to low birth weight infants. It was concluded that poor periodontal health is a potential independent risk factor for low birth weight.

Although the number of studies showing a positive correlation in terms of a possible link between periodontal disease and low birth weight is growing, some studies have demonstrated contrary findings. Davenport et al.⁴¹ found no association between maternal periodontal disease and a risk of preterm low birth weight. In another study, Michalowicz et al.⁴² suggested that periodontal progression is not associated with an increased risk for delivering a preterm or a low birth weight infant. The distribution of gestational age at the end of pregnancy and mean birth weight in Michalowicz et al.'s⁴² study did not differ significantly between women with and without periodontal disease progression. Gestational age and birth weight were not associated with a change from the baseline in the percentage of tooth sites with periodontal disease.

Interestingly, a few studies have also queried the role of periodontal therapy in reducing low birth weight. In 2009, Michalowicz et al.⁴³ studied the effect of scaling and root planing before the 21st gestational week, plus monthly tooth polishing, in 823 pregnant women in Minnesota in the USA. They did not find a significant difference between the treatment and the control groups with regard to the birth weight or in the rate of delivery of infants that were small for their gestational age. In 2010, an observational study by Calabresse et al.⁴⁵ was also unable to provide evidence of an association between periodontal disease and pre-term low birth weight. In 2011, a meta-analysis of randomized controlled trials by Baccaglini⁴⁴ showed no evidence that periodontal treatment during pregnancy could prevent adverse pregnancy outcomes. Another study in 2011 by Chambrone et al.⁴⁶ also reported that maternal periodontal disease treatment did not decrease the risk of preterm birth or of low birth weight.

In conclusion, while the review of the literature suggests that the evidence appears to be weighted in favour of a significant association between periodontal disease and preterm delivery and/or low birth weight delivery,^{7,8,47} the evidence is not unequivocal. Furthermore, most studies on this subject have been conducted using a relatively small sample size and/or have been conducted mostly in developed countries. Therefore, only limited information is available on the association between periodontal disease and low birth weight in low-income and middle-income countries, where both poor oral health and adverse reproductive outcomes are more prevalent.

1.3 SIGNIFICANCE AND RELEVANCE OF THE STUDY

In the light of the controversial results of previous investigations, and especially the possibility that a combination of biological and environmental factors may promote an association between periodontal disease and low birth weight, without a clear cause-effect relationship,⁴³ it is imperative to continue to investigate this question in order to expand our understanding of the relationship between oral health and pregnancy outcomes. This is particularly important considering that to the best of the researcher's knowledge, this is the first study to examine this relationship in a South African population.

Conducting this study is relevant to public health, because low birth weight is one of the dominant factors causing child morbidity and mortality worldwide, and the frequency of its occurrence has not been satisfactorily reduced, even in developed countries.⁴⁸ Reducing child mortality and morbidity remains one of the critical millennium development goals (MDGs).⁴⁸⁻⁵⁰ The results of this study will therefore inform the content of potential educational interventions for promoting oral health at mother and child health (MCH) clinics as envisaged in the South African oral health promotion framework (DOH, 2010),⁴⁹ and will contribute to the achievement of the health-related MDG goals in South Africa.

This study may also allow some insight into the utilization rate of dental services and the prevalence of oral health-related risk behaviour among a population of South African pregnant women.

In view of these observations, and with the aim of expanding the body of evidence on this matter, the proposed study has the objective of evaluating

whether or not there is an association between maternal periodontal disease and low birth weight.

1.4 OUTLINE OF THE STUDY

The introductory chapter has presented the background to the study, as well as a literature review of prior studies on the possible association between low birth weight and periodontal disease. The significance and relevance of the study have also been discussed. The remainder of the study is organised as follows:

- Chapter 2 sets out the aim and objectives of the study, and the research question and null hypothesis;
- Chapter 3 discusses the methodology used in the study (including the study design, study population, sample, subjects, control, data collection, data analysis, and ethical considerations);
- Chapter 4 presents the results;
- Chapter 5 discusses the results; and
- Chapter 6 contains the conclusions, and a recommendation is made.

CHAPTER 2: AIM AND OBJECTIVES OF THE STUDY

2.1 AIM OF STUDY

The aim of this study is to explore the association between periodontal disease among pregnant women and adverse reproductive outcomes in a rural population of South African women. This may inform policy aimed at improving pregnancy outcomes.

2.2 SPECIFIC OBJECTIVES

The specific objectives of this study are the following:

- to examine the association, if any, between periodontal disease in pregnant women and the delivery of low birth weight newborns;
- to determine the prevalence of oral health-related risk behaviours among pregnant women; and
- to determine the utilization rates for dental services among pregnant women in the Chris Hani District of the Eastern Cape.

2.3 RESEARCH QUESTION

The study attempts to answer the following question:

Is periodontal disease associated with a significantly increased risk for the delivery of low birth weight newborns?

2.4 HYPOTHESIS

The null hypothesis in this study is the following:

There are no significant differences in the incidence of low birth weight among women with periodontal disease compared to the incidence among periodontally healthy women.