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The Impact of Periodontal Changes during Pregnancy on Adverse Pregnancy Outcomes: A Systematic Review

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List of symbols and acronyms

ER= estrogen receptor

PgR= progesterone receptor

TNF-α= tumor necrosis factor-α

PGF2a= Prostaglandin-F2a

PD= periodontal disease

PTB= preterm birth

LBW= low birth weight

GCF= gingival crevicular fluid

PL= preterm labor

PI= plaque index

BOP= bleeding on probing

PPD= probing pocket depth

CAL= clinical attachment level

APO= adverse pregnancy outcomes

PLBW= preterm low birth weight

SPTD= spontaneous preterm delivery

Abstract

Background: The impact that periodontal changes in pregnant women have on possible APOs remains to be a controversial phenomenon yet to be proven by more studies. The objective of this study was to gather and encapsulate evidence from selected studies regarding the relationship between periodontal disease and pregnancy, whether it is a risk factor for APOs, and whether treating it could prevent APOs.

Materials and Methods: The inclusion criteria for this systematic review are cohort, randomized controlled trials, or case-control studies, articles written in English, Spanish, or German, published in the last 10 years (2000-2022). The exclusion criteria include studies regarding pregnancy not including hormonal changes, and systematic reviews. The systematic review used the databases PubMed and SCOPUS with the last search having been on April 15, 2022. In total, seven articles were selected including 2 case control studies and 5 randomized controlled trials. The CASP guide method was utilized to assess risk of bias of the selected studies. The results were presented and synthesized in a table with additional text.

Results: A total of 7 studies were included in this systematic review and a total of 958,837 participants. Relevant characteristics of the studies include the author/year of publication, type of study, sample size, definition of premature delivery and/or low birth weight, definition of periodontal disease, relative risk, aim of the study, and conclusions. 3 studies have shown that periodontal disease appears to be a risk factor for APOs such as preterm birth and/or low birth weight (LBW: 0.93 (0.91-0.94) p <0.001, PLBW: 5.49 (1.65-18.22) p = 0.001, PLBW: 7.58 (1.07-53.59) p = 0.02). 4 studies have not shown evidence in support of the claim that treating periodontitis reduces the risk of APOs (PL: 0.28 (0.02-2.98) and LBW: 0.28 (0.02-2.98), PL: 0.915 (0.561-1.1493) and LBW: 0.735 (0.459-1.179), PLBW: 7.58 (1.07-53.59) p = 0.02, PL: 1.61 (0.90-2.88) p = 0.11 and LBW: 1.38 (0.92-2.08), 0.93 (0.63-1.37) p = 0.70.

Conclusion: Limitations of this systematic review include discrepancies of definitions of periodontal disease, as well as different sample sizes between the selected studies. Though there is a clear relationship between periodontal disease and the effects it has on pregnancy, more studies are needed to prove the claim that treating periodontal disease during pregnancy can prevent APOs.

Keywords

Periodontitis, periodontal disease, periodontal health, pregnancy, pregnant women, adverse pregnancy outcomes, preterm birth, low birth weight

1. Introduction

1.1 Pregnancy

Pregnancy, the distinctive period during a woman's life, lasts an average of 40 weeks and is classified into three trimesters. The first trimester includes the first 12 weeks, the second trimester is from week 13 to 28, and the third trimester lasts from week 29 to ideally concluding pregnancy with labor and birth at week 40. Delivery of the baby before week 37 is considered a preterm birth.

During this unique time, a woman goes through many significant physiological and anatomical changes. These changes, which affect every system of the body, naturally occur to adequately foster a nurturing and protective environment for the developing fetus. Hormonal alterations are the root cause of the numerous changes a pregnant woman goes through. The principal hormones that elevate during pregnancy are progesterone and estrogen, as well as the production of the pregnancy hormone called human chorionic gonadotropin. These hormonal changes have been linked with physiological repercussions on a systemic level, as well as the possible development of adverse consequences on the periodontium and overall oral health of pregnant women (1).

1.2 Systemic Changes

Throughout pregnancy, a woman undergoes physiological changes on a systemic level. These changes include significant amendments in the cardiovascular system and its physiology, which is the body's way of adapting and responding to the metabolic changes and demands of the mother and growing fetus. The changes in the cardiovascular physiology, both intrinsic, within the uterine tissues, and extrinsic, within the mesometrium, of a pregnant woman are the body's mechanism of ensuring a sufficient uteroplacental circulation and guaranteeing the correct development and growth of the fetus (2). If the body is unable to adapt to these physiological changes orchestrated by hormonal mediators, critical consequences such as maternal and fetal morbidity, intrauterine growth retardation, preeclampsia, and may even expose an underlying cardiac pathology (2).

1.3 Cardiovascular Changes

Maternal hemodynamic changes include the vasodilation of the systemic vasculature and the maternal kidneys. This process begins at around 5 weeks, preceding the full development of the uteroplacental circulation. The intrinsic remodeling of the uterine vasculature, which is mostly, but not entirely reversible, refers to the cellular and biochemical hemodynamic alterations contributing to elevated systemic vascular resistance in hypertension and its consequences. About 2 weeks after the birth, the systemic vascular resistance decreases for the most part back to nonpregnant levels. Other hemodynamic changes occurring during pregnancy include the increase of cardiac output, with the greatest upsurge at the start of the first semester, a continuing increase throughout the second semester, and a return to normality by the third semester. Moreover, during pregnancy there is a decrease in arterial pressure, however, a recent study has found that overweight women had a higher blood pressure throughout their pregnancy. More cardiovascular changes include an increase in heart rate, with a maximum heart rate during the third trimester. Early on during a normal pregnancy, vasomotor sympathetic activity is elevated, which may result in gestational hypertension or even preeclampsia. The vasodilation during pregnancy and the increased levels of hormones, progesterone and estrogen, have a direct relationship. Relaxin, which is a peptide hormone, is produced by the corpus luteum and present during pregnancy. Relaxin has a vasodilatory role on the endothelium. Furthermore, there is an activation of the renin-angiotensin-aldosterone system during pregnancy starting in the early stages of the first trimester. As more estrogen is produced, angiotensinogen production increases as well. This results in the maintenance of blood pressure and aids in the retention of salt and water in pregnancy combating the salt and water loss due to the maternal systemic and renal arterial dilation. Progesterone, a powerful aldosterone antagonist, prevents sodium retention and hypokalemia by acting on the mineralocorticoid receptor. During pregnancy, erythropoiesis increases resulting in a surge of total blood volume, plasma volume, as well as red blood cell mass. Fetal growth is found to be directly related to plasma volume expansion, and a lack of plasma volume expansion has been directly correlated to the occurrence of preeclampsia and various pathological defects (3).

1.4 Hormonal Changes

The increase in estrogen and progesterone levels during pregnancy are thought to be a causative agent of the gingival inflammation in pregnant women, possibly leading to further periodontal pathologies. Estradiol, produced by the ovary and the placenta, is the main estrogen in plasma. Progesterone is the leading progestin, which is produced and excreted by the corpus luteum, placenta, and the adrenal cortex (2). These two hormones surge due to their constant production Plasma levels of progesterone summit to 100 ng/mL, which is 10 times higher than the peak luteal phase of the menstrual cycle (1). Estradiol may increase to 6 ng/mL, which is 30 times higher than its levels during the reproductive cycle (2). There are two theories regarding the mechanism of the possibility of the direct or indirect influence that pregnancy hormones have on periodontal ligament cells. The first one proposes that the epithelial barrier to bacteria is altered, and the other one suggests that collagen maintenance and repair is affected by the hormonal changes. Moreover, studies have put forward the theory that folate storage, which is necessary for tissue repair and maintenance, expends due to the increase of sex hormones. At high concentrations, estradiol is thought to control cellular proliferation, differentiation, keratinization, and the permeability of the microvasculature. In women, modifications of blood vessels in systemic target tissue have been linked to estrogen as a causative factor. Nonetheless, progesterone has evidently more responsibility over local vasculature in gingiva and various intraoral tissues, periodontal and non-periodontal (1). In some studies, estrogen receptors (ER) and progesterone receptors (PgR) have been observed in the human periodontium. This evidence supports the theory that these hormones target periodontal tissues. However, another study did not observe ER in the human periodontium. A lack of specificity of the techniques in the experiments explains this disparity between studies (2).

1.5 Inflammatory Changes

Moreover, changes in inflammatory markers play a significant role throughout pregnancy. Though the process of inflammation in the body is involved in the presence of disease, it is also associated with pregnancy. This inflammatory response occurs to construct and maintain a successful pregnancy. In the process of inflammation, leucocytes interconnect, cohere, and roam through the endothelium into the tissue. This is aided by cytokines, which are adhesion molecules, such as interleukins and tumor necrosis factor-α (TNF-α). This process leads to tissue edema due to the increase in vasopermeability and the influence on vascular tone. Interleukin 6 (IL-6) is a proinflammatory and anti-inflammatory cytokine, which is produced by white blood cells, fibroblasts, and endothelial cells. IL-6 is responsible for instigation of a systemic response regarding a stimulus of local inflammation. IL-6 has been seen to increase notably throughout pregnancy and this surge persisted postpartum. It has been reported that high levels of IL-6 have been found in preeclampsia in comparison to a normal pregnancy. This is explained by the fact that hypoxic conditions increase IL-6, which is believed to be connected to the endothelial cell activation and damage related to preeclampsia. Monocytes, neutrophils, and macrophages produce the proinflammatory cytokine TNF-α in placental tissues (4). Similar to IL-6, high concentrations of TNF-α have been linked to preeclampsia due to the endothelial cell activation and damage that it contributes to in hypoxic conditions. This disrupts the balance of the endothelium-derived vasoconstrictors and vasodilators, which may lead to impairment of the endothelium-dependent relaxation. Furthermore, the activation of COX leads to the in vivo formation of Prostaglandin-F2a (PGF2a), which has strong vasoconstrictive and proinflammatory properties, in physiological as well as pathophysiological situations. COX is activated during situations of inflammation and the mediators of such inflammatory reactions are the prostaglandins. In one study, it was shown that PGF2a levels were higher in pregnant women than in non-pregnant women (4).

1.6 The Periodontium and its Changes during Pregnancy

Alongside the various systemic repercussions that follow with pregnancy, the periodontium is also vastly affected. The development of periodontal changes during pregnancy is a common phenomenon. This may appear as gingivitis, which is a mild form and possible predecessor of periodontitis. Gingivitis presents itself as gingival inflammation and irritation without loss of connective tissue attachment, and most commonly appears due to the accumulation of plaque or bacteria surrounding the teeth leading to a dysbiosis of the oral microbiome. If left untreated, gingivitis may progress to periodontitis, which is severe inflammation of the gingiva with loss of connective tissue attachment and progressive bone destruction. These pregnancy symptoms are highly prevalent, affecting 60%-75% of pregnant women (1). The periodontium is the pillar that maintains and supports teeth. It is composed of the following: gingiva, periodontal ligament, alveolar bone, and cementum. The gingiva is made of up specialized epithelial tissue surrounding the teeth, which is aided by the junctional epithelial cells situated at the base of the gingival sulcus. These junctional epithelial cells serve as a barrier protecting against trauma– both mechanical and microbiological. In addition, the gingiva oversees sensation in the oral cavity as well as absorbing micronutrients. The gingiva is also a main mediator in the instigation of periodontitis, as it possesses a vital role in the innate immune response to infectious inflammation in periodontal tissue. The lamina propria, which is the gingival connective tissue, is made up of 60% collagen fibers, 5% cells, and 35% ground substance. The numerous cells include fibroblasts, mast cells, macrophages, and inflammatory cells. The principal cells are the fibroblasts, which oversee the formation of the collagen fibers and ground substance present in the connective tissue.

1.7 Periodontal Disease

1.7.1 Definition

Defining periodontal diseases (PD) as solely a bacterial infection is inaccurate. Instead, they are multifactorial compounded diseases, which include etiological factors such as environmental factors, inflammatory responses and host immune, and subgingival microbiota. Most recently, the assessment of periodontal health encompasses measurements of attachment level, probing depth, bone loss and/or degree of inflammation (5,6). Predisposing factors that may lead to the development of PD also include tooth anatomy, tooth position, restorations. These are all states that may create a susceptible environment for the formation of the bacterial biofilm, named dental plaque. Modifying factors such as smoking, systemic conditions, and medication also contribute to the emergence of periodontal disease as they change the way that the individual reacts to the accumulation of subgingival plaque. The microenvironment of the periodontium forms the bacterial configuration of the subgingival biofilm. This biofilm and its persistence are linked to gingivitis and periodontal disease. In a state of periodontal health, the microenvironment is a harmonious habitat for the commensal organisms. If the balance of the microenvironment is compromised, a dysbiosis of the microbial composition could lead to the dominance of harmful microbes, which could aggravate a state of periodontal inflammation (6). Indicators of periodontal health include bleeding on probing, periodontal probing depth, radiographic features of periodontal health, and tooth mobility. As a clinical parameter, bleeding on probing is normally assessed by bleeding instigated by the application of a probe to the base of a sulcus, or pocket. Though pocket depth may be considered as a clear indication of PD, other factors must be taken into consideration such as bleeding on probing, modifying factors, and predisposing factors. A radiography of a healthy and intact periodontium shows an unharmed lamina dura, no bone loss in furcation zones, and, on average, 2 mm from the coronal part of the alveolar bone crest to the cementoenamel junction. Teeth, physiologically, present a certain degree of mobility since they lack osseointegration, and instead are embraced by a complex webbing of collagenous fibers in the alveolar bone. The distinction between physiological and pathological mobility is defined by the magnitude of crown movement in response

to an applied force. According to various studies, PD may affect 20-50% of pregnant women. The produced hormone, relaxin, may act on the periodontal ligament and elicit an increase in tooth mobility. This tooth mobility usually dissipates postpartum. A significant bone resorption or tooth loss due to mobility during pregnancy is highly unlikely. A previously existing PD may be aggravated due to the factors previously mentioned (5).

1.7.2 Pyogenic Granuloma in Pregnancy

Pyogenic granuloma, an inflammatory lesion of the gingiva, may appear in up to 5% of pregnant women. Though this lesion may appear during any time or stage of pregnancy, it is more likely to appear during the first and second trimesters of a woman's first pregnancy. However, pyogenic granulomas, identical both clinically and histologically, may also evolve in men and non-pregnant women. It is a painless, edematous, highly vascularized lesion with interdental attachment. The lesion, which grows rapidly in size to up to 2 cm, is normally located on the upper anterior teeth. It is very rare to detect bone destruction around the teeth due to the lesion, but ulceration of its surface may occur (7). Factors such as plaque, trauma, and altered hormonal status are most likely contributed to the etiology of the lesion. The inflammatory cells of this lesion are both acute and chronic, and one study found that macrophages, which possess estrogen receptors, are greatly responsible for the inflammatory angiogenesis. The treatment of this lesion may consist of surgical excision after delivery, or during pregnancy if it is a source of problems such as functional ones or spontaneous bleeding. Removal of the lesion during pregnancy may provoke recurrency of it. More commonly, and if in a mild form, the granuloma disappears spontaneously postpartum with occasional permanent changes of the gingiva (7).

1.8 Caries

Dental caries is one of the most common oral health problems. This multifactorial disease is mediated by influential factors, which may be pathological or protective, including the presence of biofilm, excessive sugar intake, and a lack of oral hygiene. These factors determine the phasic demineralization and remineralization of teeth, which may ultimately lead to the initiation and progression of the disease. During pregnancy, women usually

experience a surge in food cravings most commonly including carbohydrates and sugars. In addition to the increased sugar intake, a reduced production of saliva and intensification of acidity in the oral cavity, the susceptibility of developing caries exponentially rises in pregnant women. A diminution of plaque pH often accompanies the decrease in saliva production, which may lead to preservation of sugars on the tooth surface. Saliva acidity has also been found in pregnant women. One study has found that the saliva pH of pregnant women is lower compared to the saliva pH of non-pregnant women (7). All these risk factors may provoke oral health consequences such as dental caries. Additionally, the neglection of oral hygiene, a lack of attending to dental visits, and disregarding necessary dental treatments aggravate the appearance of dental caries. Nausea, vomiting, and acid reflux may be reasons why pregnant women may abstain from following proper oral hygiene instructions (7).

1.9 Preterm Birth

If an infant is born prior to 37 weeks of gestation, it is considered a preterm birth (PTB). Additionally, low birth weight (LBW) is normally associated with PTB. Loss of development, morbidity, and neonatal mortality are all potential outcomes of PTB. There are multiple causes for PTB such as a premature rupture of membranes, preterm labor, or other impediments like induced labor indicated mainly by preeclampsia (8). Multiple studies have identified a possible relation between periodontal disease in expecting mothers and the incidence of PTB. PTB has various risk factors including maternal infection. Being a widespread infectious as well as inflammatory oral pathology, periodontal disease may potentially be causative of PTB as proinflammatory cytokines and bacteria appear in the bloodstream, which may affect other organs in the body. One study found augmented gingival crevicular fluid (GCF) and quantity of IL-6 and prostaglandins in women who experienced PTB compared to women who underwent full-term births. Due to the connection between clinical attachment loss, probing depth, prostaglandin levels, GCF, and PTB, periodontitis is assumed to be a probable indicator of the onset of a PTB (8).

2. Justification, Hypothesis and Objectives

2.1 Justification

Oral health is a fundamental necessity to obtain maximum quality of life. A lack of it may lead to critical oral, systemic, psychological, and social consequences. The focus on the prevention of diseases and the maintenance of health is rightfully gaining more awareness today regarding oral health, and more specifically to this systematic review, periodontal health. There are certain factors that may aggravate the decline, temporary or permanent, of periodontal health. One of these factors is the physiological state of pregnancy that a woman is in for roughly 40 weeks. In this duration of time, a woman's susceptibility to the aggravation of periodontal diseases may increase due hormonal changes. The aim of this systematic review is to evaluate the relationship between periodontal disease and pregnancy, and whether the treatment of it influences adverse outcomes of pregnancy.

2.2 Hypothesis

If a woman is undergoing hormonal changes in the physiological state of pregnancy, then the appearance of adverse alterations in periodontal health may be observed.

2.3 Objectives

2.3.1 General objective:

- Investigate the relationship between periodontal disease and pregnancy

2.3.2 Specific objective:

- Determine whether periodontal disease is a risk factor for adverse outcomes of pregnancy, such as premature birth or low birth weight
- Establish whether treatment of periodontal disease during pregnancy can prevent premature birth or low birth weight newborns.

3. Materials and Methods

This systematic review was conducted following the guidelines instituted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as the review protocol (9).

3.1 Eligibility Criteria

The PICO question was established as: Whether treating periodontal disease in the population of pregnant women influences adverse outcomes of pregnancy, compared to not treating periodontal disease during gestation.

1. Population: pregnant women
2. Intervention: periodontal treatment
3. Comparison: no periodontal treatment or periodontal treatment postpartum
4. Outcome: changes in the pregnancy outcomes

The inclusion criteria of the selected studies include the following: cohort studies, randomized controlled trials, or case-control studies. As well as articles written in English, Spanish, or German.

The exclusion criteria of the selected studies include the following: studies regarding pregnancy not including hormonal changes, and systemic reviews. Studies published before January 2000 were excluded.

3.2 Information sources and search strategy

A comprehensive search of articles was conducted in the Medline Complete and Scopus databases to obtain studies up to April 15, 2022, using the following search terms: (TITLE “periodontitis” OR TITLE “periodontal disease”) AND TITLE (“pregnancy”) OR TITLE (“pregnant women”) AND TITLE (“preterm” OR TITLE “preterm birth”)) and the following keywords: "periodontitis", "periodontal disease", "periodontal health", "pregnancy", and "pregnant women", “preterm”, “preterm birth” in combination with the Boolean operators “OR” and “AND” to acquire the articles that comprised the search terms used ("periodontitis" [MeSH terms] OR "periodontal disease" [MeSH terms] OR "periodontal health" [MeSH terms] AND "pregnancy" [MeSH terms] OR "pregnant women" [MeSH terms] AND “preterm” [MeSH terms]) OR “preterm birth” [MeSH terms])

Table 1: Consulted Databases

DATABASE	SEARCH	FILTERS	DATE	NUMBER OF ARTICLES
Medline Complete	"periodontitis" OR "periodontal disease" OR "periodontal health" AND "pregnancy" OR "pregnant women" AND “preterm” OR “preterm birth”	Publication year: 2000-2021 Language: English, Spanish, German Type of publication: adaptive clinical trial, case study, clinical study, clinical trial, comparative study, controlled	April 15, 2022	82

		clinical trial, equivalence trial, evaluation study, multicenter study, observational study, pragmatic clinical trial, randomized controlled trial		
SCOPUS	(TITLE “periodontitis” OR TITLE “periodontal disease”) AND TITLE (“pregnancy”) OR TITLE (“pregnant women”)) AND TITLE (“preterm” OR TITLE “preterm birth”))	Publication year: 2000-2022 Language: English, Spanish, German Document type: Article	April 15, 2022	370

3.3 Study selection

The selected studies were individually revised by this systematic review’s tutor considering the inclusion and exclusion criteria. Firstly, the collected data was screened for the title and abstract. Irrelevant literature and duplicate studies were eliminated. Furthermore, of the remaining studies the full-text articles were reviewed to ensure accordance with the eligibility criteria. The reasons for the elimination of certain articles that did not meet the eligibility criteria were listed.

3.4 Data Extraction

After a thorough evaluation of the selected studies, variables comprised in all the studies, which provide the adequate information necessary to respond to the mentioned objectives were summarized in a table. The variables analyzed in each of the studies included:

- Author/year of publication
- Type of study
- Sample size
- Definition of premature delivery and/or low birth weight
- Definition of periodontal disease
- Relative Risk
- Aim of the Study
- Conclusions

3.5 Quality Evaluation

The CASP guide was utilized to evaluate the quality of the information of the selected articles. This evaluation included the results of the studies, their validity, and if they were beneficial to our systematic review (10). The questions included in these questionnaires first analyze the internal validity of the study, in terms of adequacy and methodological correctness. It identifies the results and analyzes whether the results obtained in the studies can be extrapolated the patients.

4. Results

4.1 Study Selection. Flow Chart

In ***Figure 1****,* the flow chart is represented. For the identification of studies via databases and registers, 2 databases were utilized to gather the selected studies, which identified a total of 452 registers. The databases Medline Complete and SCOPUS were used, where 82 and 370 studies were identified, respectively. From these identified studies, 44 studies were removed due to being

duplicates. In total, 408 records were screened. Out of these records, 364 records were excluded due to being irrelevant to the topic. 44 registers were sought for retrieval, of which 6 reports were not retrieved. 38 reports were assessed for eligibility, of which 22 were excluded due to not providing relative risk, 6 were excluded due to not being in humans, and 3 were excluded for not including the common variables. Finally, 7 studies were included in this review.

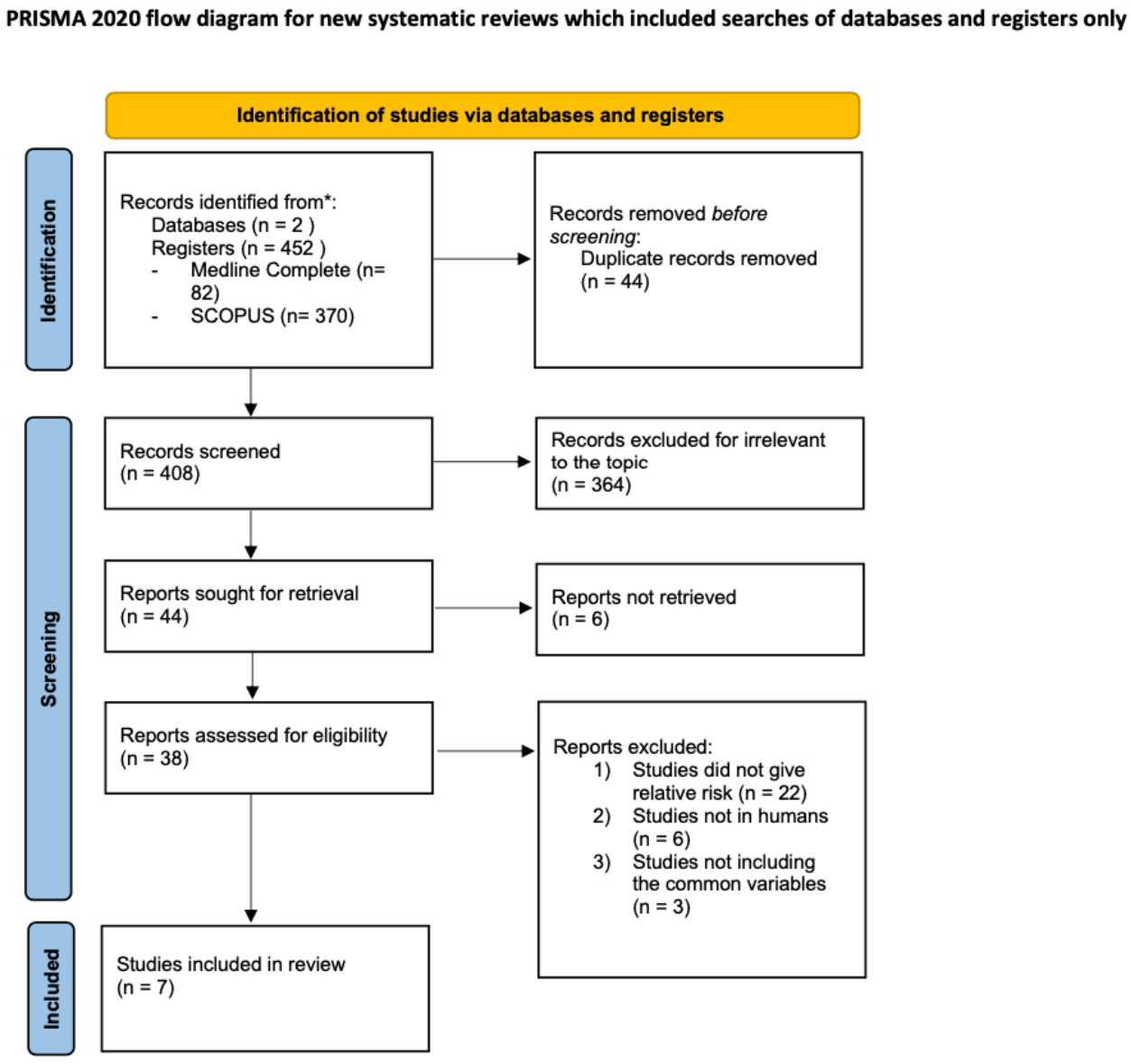

Figure 1. *Flow Diagram*

Table 1: *Characteristics of Included Studies*

Author/Year / Country	**Type of Study**	**Sample Size (n = number of participants)**	**Sample Characteristics**	**Definition of Periodontal Disease**	**Aim of the Study**	**Conclusions**
Chen et al., 2022, Taiwan (11)	Case-Control Study	n = 869,580 (non-LBW) n = 86,958 (LBW)	Age ≥ 18 years		Whether regular scaling performed prior to pregnancy improves the risk of APOs	PD is an important risk factor for preterm LBW newborns
Caneiro-Queija et al. 2019, Spain (12)	Randomized Clinical Trial	n = 40 (total) n = 20 (test group) n = 20 (control group)	Age 18-40 years < 24 weeks of gestation		Analyze if non-surgical treatment of PD can reduce APOs	Non-surgical periodontal treatment did not reduce the risk of APOs
Oliveira et al., 2010, Brazil (13)	Case-Control Study	n = 246 (total) n = 122 (non-surgical treatment during gestation) n = 124 (no treatment during gestation)	Age 18-35 years 12-20 weeks of pregnancy	Presence of four or more teeth with one or more sites with PD ≥ 4 mm and CAL ≥ 3 m	Effects of non-surgical periodontal treatment in the occurrence of APOs	Non-surgical periodontal treatment did not reduce the risk for PL or LBW
López et al., 2002, Chile (14)	Randomized Controlled Trial	n = 400 (total) n = 200 (periodontal	Age 18-35 years	Presence of 4 or more teeth with 1 or more sites with PD ≥4	Evaluate the association between	PD appears to be a risk factor for PLBW

		treatment before 28 weeks of gestation) n = 200 (periodontal treatment after delivery)	9-21 weeks of gestation	mm and with clinical attachment loss ≥3 mm at the same site	PD and PLBW	
Sant'Ana et al., 2010, Brazil (15)	Controlled Clinical Trial	n = 33 (total) n = 16 (intervention group) n = 17 (no intervention group)	Age 16-39 years old 9-24 weeks of gestation		Evaluate the effects of non-surgical treatment of PD on APOs	Periodontal treatment was associated to a decreased risk of APOs
Macones, MD et al., 2010, USA (16)	Randomized Clinical Trial	n = 757 (total) n = 378 (active group) n = 379 (control group)	Age 24.1 ± 5.2 years old (active group) Age 24.4 ± 5.7 years old (control group) 6-20 weeks of gestation	Attachment loss ≥3 mm on ≥3 teeth Moderate/Severe: Attachment loss of ≥ 5 mm on ≥ 3 teeth	Whether treating PD in pregnancy will reduce the incidence of SPTD	Treating PD does not reduce the incidence of SPTD

Michalowicz, D.D.S. et al., 2006, USA (17)	Randomized Controlled Trial	n = 823 (total) n = 413 (treatment group) n = 410 (control group)	13-17 weeks of gestation	4 or more teeth with a probing depth of at least 4 mm and a clinical attachment loss of at least 2 mm, as well as bleeding on probing at 35% or more of tooth sites	Effect of non-surgical periodontal treatment on preterm birth	Treatment of PD does not significantly alter rates PB or LBW

PD= Periodontal disease. PB= Preterm birth. PL= Preterm labor. LBW= Low Birth Weight. PLBW= Preterm Low Birth Weight. SPTD= Spontaneous Preterm Delivery.

In ***Table 1***, the primary characteristics of the included studies were demonstrated. This systematic review includes 7 studies. Of these 7 studies, 2 were case-control studies and 5 were randomized controlled trials. 2 of the 7 studies were conducted in the USA, 2 further studies in Brazil, 1 study in Taiwan, 1 study in Spain, and 1 study in Chile. The total amount of participants in this study is 958,837 women. On average, the gestation period of all the studies was between 6-24 weeks and the age was between 16-40 years. Sant;Ana (15) had the lowest age of participants, including 16 years as the minimum. Michalowicz, D.D.S. et al. (17) is the only study among all the selected studies that does not mention the age of the participants. The case-control study by Chen et al. (11) has the largest sample size of all the included studies, reaching a total of 956,538 participants in both groups, non-LBW and LBW, combined. Sant'Ana et al. (15) has the smallest sample size of all the included studies, with a total of 33 participants, 16 in the intervention group and 17 in the no intervention group. Out of the 7 studies, 4 included definitions of periodontal disease and 3 studies omitted this characteristic of their studies. Oliveira et al. (13) stated the definition of periodontal disease equal to the definition stated by López et al. (14). Macones et al. (16) and Michalowicz et al. (17) had different definitions of periodontal disease. Chen et al. (11), Caneiro-Queija et al. (12), and Sant'Ana (15) did not mention any definition of periodontal disease in their studies. 6 of the 7 studies

had the same definition of preterm labor, which was labor before 37 weeks of gestation. 1 study, Macones, MD et al. (16), defined preterm labor as labor before 35 weeks of gestation. 6 of the 7 studies had the same definition of preterm labor, which was labor before 37 weeks of gestation. 1 study, Macones, MD et al. (16), defined preterm labor as labor before 35 weeks of gestation. Low birth weight has been defined as <2,500 g, which is an equal definition across all the included studies. 2 studies, Oliveira et al. (13) and López et al. (14), had the same definition of periodontal disease. See ***Table 2*** and ***Table 3*** for the results of the objectives of this systematic review.

4.3 Evaluation of Bias

Table 3. *CASPe checklist for Case Control Studies*

	Chen et al., 2022 (11)	Oliveira et al., 2010 (13)
1. Did the study address a clearly focused issue?	Yes	Yes
2. Did the authors use an appropriate method to answer their question?	Yes	Yes
3. Were the cases recruited in an acceptable way?	Yes	Yes
4. Were the controls selected in an acceptable way?	Yes	Yes
5. Was the exposure accurately measured to minimize bias?	Yes	Yes
6. (a) Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
(b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes	Yes
7. How large was the treatment effect?	The treatment effect was significant as the end results showed a clear conclusion to the objective of the study	The treatment effect was less significant as the conclusion did not support the hypothesis
8. How precise was the estimate of the treatment effect?	The estimate of the treatment effect is significantly precise, as shown by the p-value	The estimate of the treatment effect is not very precise, as the wide confidence intervals indicate
9. Do you believe the results?	Yes	Yes

10. Can the results be applied to the local population?	Can't Tell	Can't Tell
11. Do the results of this study fit with other available evidence?	Yes	Yes

Table 4. *CASPe checklist for Randomized Controlled Trial*

	López et al., 2002 (14)	Caneiro-Queija et al. 2019 (12)	Macones, MD et al., 2010 (16)	Michalowicz, D.D.S. et al., 2006 (17)	Sant'Ana et al., 2010 (15)
1. Did the study address a clearly focused research question?	Yes	Yes	Yes	Yes	Yes
2. Was the assignment of participants to interventions randomized?	Yes	Yes	Yes	Yes	Yes
3. Were all participants who entered the study accounted for at its conclusion?	No	No	No	No	No
4. • Were the participants 'blind' to intervention they were given?	Can't Tell	Can't Tell	Yes	No	Can't Tell
• Were the investigators 'blind' to the intervention they were giving to participants?	No	No	No	No	No
• Were the people assessing/analyzing outcome/s 'blinded'?	No	No	No	No	No
5. Were the study groups similar at the start of the randomized controlled trial?	Yes	Yes	Yes	Yes	Yes
6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	Yes	Yes	Yes	Yes	Yes
7. Were the effects of intervention reported comprehensively?	Yes	Yes	Yes	Yes	Yes
8. Was the precision of the estimate of the intervention or treatment effect reported?	Yes	Yes	Yes	Yes	Yes
9. Do the benefits of the experimental intervention outweigh the harms and costs?	Yes	Yes	Yes	Yes	Yes

10. Can the results be applied to your local population/in your context?	Yes	Yes	Yes	Yes	Yes
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Yes	Yes	Yes	Yes	Yes

4.4 Synthesis of Results

In ***Table 2***, the author, year, and country of each study is listed. Furthermore, the sample size and sample characteristics, which include the age and the weeks of gestation, if available. The total sample size of the selected studies for this objective is 956,938 participants. Chen et al. (11) had a large sample size with 956,538 participants overall. The women in this study were divided into groups of non-LBW and LBW newborns. López et al. (14) had a sample size of 400 participants, and the women in this study were divided into two equal groups of 200, one group received periodontal treatment before 28 weeks of gestation and the other group received periodontal treatment after delivery (14). The age among the two studies is between 18-35 years. The maximum possible age for participants in the study by López et al. (14) was 35 years. 1 of the studies, López et al. (14), mentioned the weeks of gestation, which were between 9-21 weeks. The other study by Chen et al. (11) did not mention the weeks of gestation.

Table 2: *Measurement of risk of APOs due to PD during pregnancy*

Author	**Year**	**Country**	**Sample Size (n = number of participants)**	**Sample Characteristics**	**Definition of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Spontaneous Preterm Delivery (SPTD)**	**Relative risk (RR) (95% CI) of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Preterm/Low Birth Weight (PLBW)**
Chen et al. (11)	2022	Taiwan	n = 869,580 (non-LBW) n = 86,958 (LBW)	Age ≥ 18 years	PL: <37 weeks of gestation LBW: <2,500 g	LBW: 0.93 (0.91-0.94) p <0.001
López et al. (14)	2002	Chile	n = 400 (total) n = 200 (periodontal	Age 18-35 years	PL: < 37 weeks LBW: < 2,500 g	PL: 5.48 (1.17-27.71) p = 0.014

			treatment before 28 weeks of gestation) n = 200 (periodontal treatment after delivery)	9-21 weeks of gestation		LBW: 6.26 (0.73-53.78) p = 0.052 PLBW: 5.49 (1.65-18.22) p = 0.001

In ***Table 2,*** the studies by Chen et al. (11) and López et. al (14) were conducted in 2022 in Taiwan and in 2002 in Chile, respectively. The definitions of PL as well as LBW are mentioned for each other included studies. The definition of PL is equal among the two studies, as well as the definition of LBW. PL is stated as <37 weeks in both included studies, and LBW is stated as <2,500 g in both included studies. Furthermore, it is shown that all the included studies used relative risk in a confidence interval of 95% to determine their results. The study conducted by Chen et al. (11) assessed whether regular scaling performed prior to pregnancy improves the risk of APOs, in this case LBW. The outcome of this study is represented by a confidence interval of 0.93 (0.91-0.94) and a p value of <0.001. This is a precise interval, which strongly proves that PD is an important risk factor for preterm LBW newborns (11). The randomized controlled trial directed by López et al. (14) assessed the association between PD and PLBW. The result of this study was demonstrated by the relative risk. The authors found a relative risk of 5.49 in a 95% confidence interval of 1.65-18.22 and a p value of 0.001, clearly showing that PD can be considered a risk factor for PLBW. Both studies show that PD is a risk factor for APOs, such as LBW or PLBW. See ***Table 3*** for the analysis regarding whether treatment of periodontal disease influences the risk of APOs.

Table 3: *Measurement of risk whether periodontal treatment is associated to APOs*

Author	Year	Country	Sample Size (n = number of participants)	Sample Characteristics	Definition of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Spontaneous Preterm Delivery (SPTD)	Relative risk (RR) (95% CI) of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Preterm/Low Birth Weight (PLBW)
Caneiro-Queija et al. (12)	2019	Spain	n = 40 (total) n = 20 (test group) n = 20 (control group)	Age 18-40 years < 24 weeks of gestation	PL: <37 weeks of gestation LBW: <2,500 g	PL: 0.28 (0.02-2.98) LBW: 0.28 (0.02-2.98)
Oliveira et al. (13)	2010	Brazil	n = 246 (total) n = 122 (non-surgical treatment	Age 18-35 years 12-20 weeks of pregnancy	PL: <37 weeks of gestation LBW: < 2,500 g	PL: 0.915 (0.561-1.1493) LBW: 0.735 (0.459-1.179)
Sant'Ana et al. (15)	2010	Brazil	n = 33 (total) n = 16 (intervention group) n = 17 (no intervention group)	Age 16-39 years old 9-24 weeks of gestation	PL: < 37 weeks LBW: <2,500 g	PLBW: 7.58 (1.07-53.59) p = 0.02
Macones, MD et al. (16)	2010	USA	n = 757 (total) n = 378 (active group)	Age 24.1 ± 5.2 years old (active group) Age 24.4 ± 5.7 years old (control group)	SPTD: ≤ 35 weeks LBW: 2,500 g	PL: 1.61 (0.90-2.88) p = 0.11 LBW: 1.38 (0.92-2.08)

			n = 379 (control group)	6-20 weeks of gestation	PL: < 35 weeks	
Michalowicz, D.D.S. et al. (17)	2006	USA	n = 823 (total) n = 413 (treatment group) n = 410 (control group)	13-17 weeks of gestation	PL: < 37 weeks LBW: < 2,500 g	Treatment group vs. control group: 0.93 (0.63-1.37) p = 0.70

Table 3 analyzes the results of whether treatment of periodontal disease has an influence on the risk of APOs. 5 out of 7 studies did not find that treatment of PD altered or decreased the risk or rates of PB and/or LBW. The studies were published between 2006 to 2019. The studies were published between 2006 to 2019. 1 study was realized in Spain, 2 studies in Brazil, and 2 studies were conducted in the USA. The total number of sample size between all the studies is 1,899 participants. The study with highest number of participants is by Michalowicz et al. (17) with a total of 823 participants. The lowest number of participants is by Sant'Ana et al. (15) with a total of 33 participants. The age range between all the participants in the selected studies is between 16-40 years. The period of gestation is between 6-24 weeks of gestation between all the included studies. PL is defined as labor <37 weeks among all the selected studies in this table. LBW is defined as <2,500 g among all the selected studies in this table. All the included studies used relative risk in a 95% confidence interval to assess the risk of PL, LBW, or PLBW of all the included studies. The aim of all the selected studies in this table was to analyze whether non-surgical treatment of PD during pregnancy can alter or reduce the risk or occurrence of APOs such as PB or LBW. Out of the 5 studies in this table, only 1 study affirmed that periodontal treatment was associated to a decreased risk of APOs. 4 out of 5 studies have shown that treatment of PD does not alter or reduce the risk of APOs such as PB or LBW. The randomized clinical trial by Caneiro-Queija et al. (12) had a total of 40 participants, divided equally into a test group and a control group. The

maximum age of participants was 40 years, and the maximum weeks of gestation was 24 weeks. This study analyzed whether non-surgical treatment of PD can reduce APOs, such as PB or LBW. The results were measured using relative risk in a 95% confidence interval. The authors did not find that the relative risk was significant, and the null hypothesis was not able to be rejected. This left the authors with a conclusion that non-surgical periodontal treatment did not reduce the risk of APOs (12). In the study by Oliveira et al. (13), with a total of 246 participants, divided in two groups, 122 participants who received non-surgical treatment during gestation, and 124 participants who received no treatment during gestation. The maximum age of participants was 35 years, and the weeks of gestation were between 12-20. The authors did not find precise values of relative risk, leaving them with a result that non-surgical periodontal treatment did not reduce the risk for PL or LBW (13). Sant'Ana et al. (15) had a total of 33 participants, with 16 in the intervention group and 17 in the no intervention group. The maximum age was 39 for the participants and the weeks of gestation between 9-24. The authors concluded, due to precise values of relative risk, that periodontal treatment was associated to a decreased risk of APOs. Macones et al. (16) conducted a randomized clinical trial with a total of 757 participants, with 378 in the active group and 379 in the control group. The weeks of gestation were between 6-20. The authors found that treating PD does not reduce the incidence of SPTD (16). Michalowicz et al. (17) realized a randomized controlled trial with a total of 823 partiicpants, 413 in the treatment group and 410 in the control group. The maximum weeks of gestation of the participants is 17 weeks. The authors assessed whether non-surgical periodontal treatment influences preterm birth, and they concluded that treatment of PD does not significantly alter rates of PB or LBW (17).

5. Discussion

Throughout recent years, there has been a surge of evidence and studies regarding the relationship between periodontal disease and how it may affect systematic health status of a person. The increased risk of systemic diseases that may come with a deteriorated oral health status has been tested in multiple studies. Additionally, the systematic effects and consequences that a woman endures during pregnancy, such as hormonal and physiological changes have also been confirmed by copious studies. These findings have led to a recently discovered phenomenon, which is the relationship between periodontal disease during pregnancy, the treatment of it, and how it is related to various adverse pregnancy outcomes. These adverse pregnancy outcomes may include preterm labor, low birth weight, preeclampsia, and more. However, the most prominent adverse outcome has been preterm labor. The main factor which has been seen to link the relationship between periodontal disease during pregnancy and preterm labor has been the influx of pregnancy hormones, mainly estrogen and progesterone, which causes a significant increase in blood supply to gum tissue, which may lead to inflammation and bleeding of the gums (2).

With the obtained results from the 7 studies included in this systematic review, it cannot be stated that treating periodontal disease reduces the risk of adverse pregnancy outcomes, such as preterm labor. Due to the differences between the findings of the studies, it is necessary to fulfill more studies and gather additional evidence to prove the direct relationship between periodontal disease during pregnancy, the treatment of it, and how it may affect pregnancy outcomes.

It can be said that the authors Chen et al. (11) have clearly proven, through their findings, that periodontal disease during pregnancy is an important risk factor for preterm low birth weight newborns. In this study, the authors have hypothesized that adverse pregnancy outcomes are associated with periodontal diseases due to the induction of a chronic systematic inflammatory response. They have compared the risk of adverse pregnancy outcomes in women with and without periodontal disease to verify whether regular scaling performed prior to

pregnancy improves the risk of adverse pregnancy outcomes. Regarding the aim of the study, the authors have obtained a p value of <0.001, which ultimately has rejected the null hypothesis of their study therefore proving the stated hypothesis that the authors have claimed in the aim of the study. Furthermore, the relative risk of low birth weight was 0.93 in a 95% confidence interval of 0.91-0.94 (11). Once again, due to these results it is possible to reject the null hypothesis. The findings of this study have proven that the risk of adverse pregnancy outcomes, specifically low birth weight, significantly increased in women who underwent periodontal treatment, making periodontal disease a risk factor for low-birth-weight newborns. This was noted when the results revealed that compared with the control group, the women who had scaling treatment within 2 years before pregnancy or during pregnancy had a lower risk of delivering low-birth-weight newborns (11).

Chen et al. (11) have indicated various statistics while evaluating the prevalence of adverse pregnancy outcomes in women who had given birth to low-birth-weight newborns in comparison to women who had given birth to non-low birth weight newborns. Significant discrepancies were seen due to differences in income, urbanization of residence, model of delivery, maternal comorbidities, and pregnancy-related complications. In the group of women who gave birth to low-birth-weight newborns, higher incidences of cesarean section, diabetes mellitus, hypertension, and hyperlipidemia were observed. This demonstrates the importance and relevance of systematic health status and the effect it has on pregnancy. And since oral health has an indisputable effect on the systematic health status, it can be said that periodontal changes during pregnancy lead to systematic, physiological changes inevitably affecting outcomes of pregnancy (11).

On the other hand, in the study conducted by authors Caneiro-Queija et al. (12), non-surgical periodontal treatment did not reduce the risk of adverse pregnancy outcomes, such as preterm birth and/or low-birthweight. Their results concluded a relative risk of 0.28 in a 95% confidence interval of 0.02-2.98 for preterm labor and a relative risk of 0.28 in a 95% confidence interval of 0.02-2.98 (12). According to these findings, the null hypothesis cannot be rejected therefore this study cannot conclude that non-surgical treatment of periodontitis in pregnant

women can reduce adverse pregnancy outcomes. Ultimately, Caneiro-Queija et al. (12) did not observe any significant differences for the variables preterm birth and/or low-birthweight of their study. Unlike Chen et al. (11) who had observed noteworthy differences between pregnant women in various living situations, such as urbanization of residence, Caneiro-Queija et al. (12) did not observe any statistically substantial dissimilarities among these groups. Oliveira et al. (13) and Michalowicz et al. (17) also supported this finding in the results of their studies. These authors have established that the treatment of periodontitis in pregnant women is safe, however, it did not reduce the incidence of premature labor and/or low birthweight. Caneiro-Queija et al. (12) analyzed the presence of periodontopathogens. The authors found that the non-surgical periodontal treatment reduced the number of the subgingival periodontal pathogens, as well as the complete bacterial load. This indicates that periodontal treatment of pregnant women with periodontitis produces quantitative and qualitative changes regarding microbiota, which are analogous to those seen in non-pregnant women (12). Various studies have presented results, which harbor discrepancies among them. Some of which indicating that the periodontopathogens may be responsible for adverse pregnancy outcomes, and some studies demonstrating the opposite. Caneiro-Queija et al. (12) have not seen that treating periodontal disease, and the removal of a percentage of these periodontopathogens, has reduced possible risks of adverse pregnancy outcomes (12).

Comparable to Caneiro-Quejia et al (12), the authors Oliveira et al. (13) have stated that non-surgical periodontal treatment during the second semester of gestation did not reduce the risk for adverse pregnancy outcomes, such as preterm birth, low birth weight, and preterm low birth weight. The relative risk for preterm labor was found to be 0.915 in a 95% confidence interval of 0.561-1.1493 (13). Moreover, the relative risk for low birth weight was 0.735 in a 95% confidence interval of 0.459-1.179 (13). With these findings, the null hypothesis cannot be rejected therefore it was not proven that non-surgical periodontal treatment may reduce the risk for adverse pregnancy outcomes. Oliveira et al. (13) found that non-surgical periodontal treatment during the second semester of gestation did not reduce the risk for preterm birth, low birth weight, and preterm low birth weight. Oliveira et al. (13) demonstrated periodontal variables in

baseline and final examinations. These periodontal variables included bleeding on probing, pocket depth, and clinical attachment level. During baseline examinations, the periodontal variables were worse in the intervention group compared with the control group. At the final examination, there was a worsening in the clinical parameters regarding periodontal variables seen in the control group. In the intervention group, an improvement was seen regarding the periodontal parameters measured. However, since the relative risk included the null in the 95% confidence interval, the estimates were considered insignificant. Therefore, no reduction of risk was seen regarding adverse pregnancy outcomes (13).

However, the authors López et al. (14) have stated that periodontal disease appears to be a risk factor for PLBW. The results obtained in this study are like the ones obtained by authors Chen et al. (11). The relative risk of preterm low birth weight newborns was 5.49 in a 95% confidence interval of 1.65-18.22 (14). Additionally, the authors have stated a p value of 0.001 regarding these results. It can be said that the null hypothesis can be rejected and that the study has proven that periodontal disease appears to be an independent risk factor for preterm low birth weight newborns. López et al. (14) have found that periodontal therapy considerably diminishes the rates of preterm low birth weight in their target population of women with periodontal disease. The authors have examined multiple clinical parameters such as oral hygiene status, gingival inflammation, probing depth, and clinical attachment level. The periodontal therapy provided consisted of plaque control instructions, scaling, and root planning performed under local anesthesia. The authors found that women with preterm low birth weight had drastically more gingival inflammation and poorer periodontal status compared to women with normal births. The population of this study was homogeneous, as the samples were taken equally regarding age and demographic characteristics. López et al. (14) concluded that regarding preterm low birth weight, periodontal disease is an independent risk factor and motions more than a 4-fold upsurge of the risk (14). Additionally, the authors found various risk factors associated with the adverse pregnancy outcomes, such as a history of preterm low birth weight, less than 6 prenatal visits, and a low maternal weight gain. Ultimately, the authors discovered that periodontal therapy significantly

reduces the rate of preterm low birth weight in women with periodontal disease (14).

The authors Sant'Ana et al. (15) have stated that periodontal treatment was associated to a decreased risk of adverse pregnancy outcomes. The objective of this study was to evaluate the effects of non-surgical treatment of periodontal disease on adverse pregnancy outcomes. Like the study conducted by López et al. (14), the relative risk of preterm low birth weight was found by the authors Sant'Ana et al. (15). The relative risk measured to be 7.58 for preterm low birth weight in a 95% confidence interval of 1.07-53.59. Additionally, they found the p value to be 0.02. The null hypothesis was rejected, and the aim of their study was proven. Sant'Ana et al. (15) evaluated their patients based on various clinical parameters, including pocket probing depth, clinical attachment level, sulcus bleeding index, and plaque index. During the second trimester of pregnancy, the patients in the intervention group showed a well-defined steadying of the periodontal parameters, while the non-intervention group showed a clear deterioration of periodontal conditions. Periodontal treatment consisted of non-surgical therapy performed at the second trimester, as well as the utilization of chlorhexidine mouthwashes at 0.12% (15). Untreated patients showed a significant worsening of periodontal conditions during pregnancy, which can conclude that the absence of periodontal treatment in patients with periodontitis can be considered as a risk factor for adverse pregnancy outcomes, especially preterm birth and/or low birth weight.

Moreover, the randomized clinical trial published by authors Macones et al. (16) concluded that treating periodontal disease does not reduce the incidence of spontaneous preterm delivery. The aim of their study was to test whether treating periodontal disease in pregnancy will reduce the incidence of spontaneous preterm delivery. The relative risk for preterm labor was 1.61 in a 95% confidence interval of 0.90-2.88. Additionally, the p value measured to be 0.11. Furthermore, the relative risk of low birth weight was 1.38 in a 95% confidence interval of 0.92-2.08 (16). These results did not confirm the proposed hypothesis, and it is not possible to reject the null hypothesis of this study. Therefore, it was not proven that treatment of periodontal disease may reduce the incidence of spontaneous preterm delivery. Patients in this study were

assigned to receive periodontal treatment. In the active group, the treatment consisted of scaling and root planning. In the control group, the treatment consisted of superficial cleaning. Macones et al. (16) have stated that they did not find evidence that the active treatment improved pregnancy outcomes. Between the two groups, there was no difference in the incidence of spontaneous preterm delivery, nor was there a difference in birthweight. These results are conversely proportional to those of López et al. (14), who found a marked reduction in the rates of preterm birth. Conclusively, Macones et al. (16) found results that do not support the treatment of periodontal disease in pregnancy with the objective of reducing the risk of preterm birth (16).

Like the authors Macone et al. (16) have mentioned, the authors Michalowicz et al. (17) have detailed that the treatment of periodontal disease does not significantly alter rates of preterm birth or low birth weight. This randomized clinical trial has a relative risk of 0.93 in a 95% confidence interval of 0.63-1.37, and a p value of 0.70 (17). These results were based off the comparison between the treatment group and the control group. However, with these results, the study was not able to prove that non-surgical periodontal treatment alters the rate of preterm birth and low birth weight. In this study, treatment of periodontal disease consisted of up to four visits of periodontal scaling and root planing. The authors found that scaling and root planing before 21 weeks of gestation as well as monthly tooth polishing did not significantly alter the risk of preterm delivery, nor did it increase birth weight. Conclusively of this study, treating periodontal disease in patients is safe, however it does not alter the rates of adverse pregnancy outcomes (17).

The discrepancies between the results of the studies further suggest the requirement for more precise studies and trials to be conducted to reach a clear consensus about the direct association between periodontal disease, the treatment of it, and how it may affect adverse pregnancy outcomes. The connection between the two factors remains a controversy. In this systematic review, 3 out of 7 studies concluded that there is an association between the treatment of periodontal disease and the improvement adverse pregnancy outcomes, as well as periodontitis being an independent risk factor for adverse pregnancy outcomes, especially preterm birth and/or low birth weight.

In the systematic review by authors Teshome et al. (18), similar results have been found regarding the relationship between periodontal disease and preterm low birth weight. This study presented inconsistent definitions of periodontal disease as well as no follow ups in some of the studies included as their limitations. Teshome et al. (18) stated that 9 of their included studies showed that PD is associated with LBW and PB. Teshome et al. (18) states that periodontal disease may be one of the potential risk factors for preterm low birth weight. Nonetheless, more detailed studies with adequate follow-ups are needed to confirm the connection (18).

In the cross-sectional study conducted by Muwazi et al. (19), the association between periodontal diseases in postpartum mothers and PTB and LBW newborns was assessed. The authors found there is a significant association between gingival recession and low birth weight (19).

In the case-control study by Uwambaye et al. (20), the association between periodontitis and premature birth. The results of this study have shown that periodontitis is pungently associated with premature birth (20).

Limitations of this systematic review include the inconsistencies between the definitions of periodontal disease among the various included studies. Apart from the differences among the definitions, 3 studies did not include any definition of periodontal disease. To eliminate this limitation, the definition of periodontal disease could be removed from the study characteristics. Additionally, another limitation is that one study includes a different definition of preterm labor than the other studies. Furthermore, data synthesis was limited to relative risk and p value, including 7 studies. This is a limitation as more studies should include a wider variety of variables. Another limitation of this systematic review is the discrepancy between sample sizes across the included studies. Some studies have proportionally smaller sample sizes than other studies. Additionally, 1 study, Chen et al. (11) does not include the weeks of gestation as part of the sample characteristics. Another limitation of this systematic review is that it is only including two databases. With more than two databases, the probability of finding more relevant articles for this systematic review rises.

6. Conclusion

- The association between periodontal disease and pregnancy has been proven by various studies, however, more studies are necessary to confirm this relationship due to the discrepancy between the results of the included studies.
- This systematic review has shown that periodontal disease can be considered a risk factor for adverse pregnancy outcomes, such as preterm birth and/or low birth weight.
- The presented evidence does not consequently verify whether treatment of periodontal disease in pregnant women could prevent adverse outcomes of pregnancy. More studies are needed to support this claim.

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8. Annexes

8.1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	12
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	12
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	13
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	14-15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	14-15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	16
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	16
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or	-

Section and Topic	Item #	Checklist item	Location where item is reported
		synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	17
Study characteristics	17	Cite each included study and present its characteristics.	18-20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	22-25
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	26-29
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	31-37
	23b	Discuss any limitations of the evidence included in the review.	37
	23c	Discuss any limitations of the review processes used.	37
	23d	Discuss implications of the results for practice, policy, and future research.	37

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

8.2 Article

Journal Selection: Periodontology

Publication Type: Systematic Review

The impact of Periodontal Changes during Pregnancy on Adverse Pregnancy Outcomes: A Systematic Review

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ABSTRACT

Background: The objective of this study was to gather and encapsulate evidence from selected studies regarding the relationship between periodontal disease and pregnancy, whether it is a risk factor for APOs, and whether treating it could prevent APOs.

Materials and Methods: The inclusion criteria for this systematic review are cohort, randomized controlled trials, or case-control studies, articles written in English, Spanish, or German. The exclusion criteria include studies regarding pregnancy not including hormonal changes, and systematic reviews. The systematic review used the databases PubMed and SCOPUS with the last search having been on April 15, 2022. In total, seven articles were selected including 2 case control studies and 5 randomized controlled trials.

***Results*:** A total of 7 studies were included in this systematic review and a total of 958,837 participants. 3 studies have shown that periodontal disease appears to be a risk factor for APOs such as preterm birth and/or low birth weight (LBW: 0.93 (0.91-0.94) p <0.001, PLBW: 5.49 (1.65-18.22) p = 0.001, PLBW: 7.58 (1.07-53.59) p = 0.02). 4 studies have

not shown evidence in support of the claim that treating periodontitis reduces the risk of APOs (PL: 0.28 (0.02-2.98) and LBW: 0.28 (0.02-2.98), PL: 0.915 (0.561-1.1493) and LBW: 0.735 (0.459-1.179), PLBW: 7.58 (1.07-53.59) p = 0.02, PL: 1.61 (0.90-2.88) p = 0.11 and LBW: 1.38 (0.92-2.08), 0.93 (0.63-1.37) p = 0.70.

***Conclusion*:** Though there is a clear relationship between periodontal disease and the effects it has on pregnancy, more studies are needed to prove the claim that treating periodontal disease during pregnancy can prevent APOs.

***Keywords*:** periodontitis, periodontal disease, periodontal health, pregnancy, pregnant women, adverse pregnancy outcomes, preterm birth, low birth weight

INTRODUCTION

Pregnancy, the distinctive period during a woman's life, lasts an average of 40 weeks and is classified into three trimesters. The first trimester includes the first 12 weeks, the second trimester is from week 13 to 28, and the third trimester lasts from week 29 to ideally concluding pregnancy with labor and birth at week 40. Delivery of the baby before week 37 is considered a preterm birth.

During this unique time, a woman goes through many significant physiological and anatomical changes. These changes, which affect every system of the body, naturally occur to adequately foster a nurturing and protective environment for the developing fetus. Hormonal alterations are the root cause of the numerous changes a pregnant woman goes through. The principal hormones that elevate during pregnancy are progesterone and estrogen, as well as the production of the pregnancy hormone called human chorionic gonadotropin. These hormonal changes have been linked with physiological repercussions on a systemic level, as well as the possible development of adverse consequences on the periodontium and overall oral health of pregnant women (1).

Throughout pregnancy, a woman undergoes physiological changes on a systemic level. The changes in the cardiovascular physiology, both intrinsic, within the uterine tissues, and extrinsic, within the mesometrium, of a pregnant woman are the body's mechanism of ensuring a sufficient uteroplacental circulation and guaranteeing the correct development and growth of the fetus (2). Maternal hemodynamic changes include the vasodilation of the systemic vasculature and the maternal kidneys. The vasodilation during pregnancy and the increased levels of hormones, progesterone, and estrogen, have a direct relationship (3).

The increase in estrogen and progesterone levels during pregnancy are thought to be a causative agent of the gingival inflammation in pregnant women, possibly leading to further periodontal pathologies (2). In women, modifications of blood vessels in systemic target tissue have been linked to estrogen as a causative factor. Nonetheless, progesterone has evidently more responsibility over local vasculature in gingiva and various intraoral tissues, periodontal and non-periodontal (1). In some studies, estrogen receptors (ER) and progesterone receptors (PgR) have been observed in the human periodontium. This evidence supports the theory that these hormones target periodontal tissues (2).

Interleukin 6 (IL-6) is a proinflammatory and anti-inflammatory cytokine, which is produced by white blood cells, fibroblasts, and endothelial cells. IL-6 is responsible for instigation of a systemic response regarding a stimulus of local inflammation. IL-6 has been seen to increase notably throughout pregnancy and this surge persisted postpartum. It has been reported that high levels of IL-6 have been found in preeclampsia in comparison to a normal pregnancy (4).

Alongside the various systemic repercussions that follow with pregnancy, the periodontium is also vastly affected. The development of periodontal changes during pregnancy is a common phenomenon. This may appear as gingivitis, which is a mild form and possible predecessor of periodontitis (1).

If an infant is born prior to 37 weeks of gestation, it is considered a preterm birth (PTB). Additionally, low birth weight (LBW) is normally associated with PTB. Multiple studies have identified a possible relation between periodontal disease in expecting mothers and the incidence of PTB. PTB has various risk factors including maternal infection. Being a widespread infectious as well as inflammatory oral pathology, periodontal disease may potentially be causative of PTB as proinflammatory cytokines and bacteria appear in the bloodstream, which may affect other organs in the body. The aim of this systematic review is to evaluate the relationship between periodontal disease and pregnancy, and whether the treatment of it influences adverse outcomes of pregnancy (5).

MATERIALS AND METHODS

This systematic review was conducted following the guidelines instituted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as the review protocol (6).

The PICO question was established as: Whether treating periodontal disease in the population of pregnant women influences adverse outcomes of pregnancy, compared to not treating periodontal disease during gestation.

1. Population: pregnant women
2. Intervention: periodontal treatment
3. Comparison: no periodontal treatment or periodontal treatment postpartum
4. Outcome: changes in the pregnancy outcomes

The inclusion criteria of the selected studies include the following: cohort studies, randomized controlled trials, or case-control studies. As well as articles written in English, Spanish, or German.

The exclusion criteria of the selected studies include the following: studies regarding pregnancy not including hormonal changes, and systemic reviews. Studies published before January 2000 were excluded.

A comprehensive search of articles was conducted in the Medline Complete and Scopus databases to obtain studies up to April 15, 2022, using the following search terms: (TITLE “periodontitis” OR TITLE “periodontal disease”) AND TITLE (“pregnancy”) OR TITLE (“pregnant women”) AND TITLE (“preterm” OR TITLE “preterm birth”)) and the following keywords: "periodontitis", "periodontal disease", "periodontal health", "pregnancy", and "pregnant women", “preterm”, “preterm birth” in combination with the Boolean operators “OR” and “AND” to acquire the articles that comprised the search terms used ("periodontitis" [MeSH terms] OR "periodontal disease" [MeSH terms] OR "periodontal health" [MeSH terms] AND "pregnancy" [MeSH terms] OR "pregnant women" [MeSH terms] AND “preterm” [MeSH terms]) OR “preterm birth” [MeSH terms])

The selected studies were individually revised by this systematic review's tutor considering the inclusion and exclusion criteria. Firstly, the collected data was screened for the title and abstract. Irrelevant literature and duplicate studies were eliminated. Furthermore, of the remaining studies the full-text articles were reviewed to ensure accordance with the eligibility criteria. The reasons for the elimination of certain articles that did not meet the eligibility criteria were listed. ***(See Figure 1)***

The variables analyzed in each of the studies included:

- Author/year of publication
- Type of study
- Sample size
- Definition of premature delivery and/or low birth weight
- Definition of periodontal disease
- Relative Risk
- Aim of the Study
- Conclusions

RESULTS

For the identification of studies via databases and registers, 2 databases were utilized to gather the selected studies, which identified a total of 452 registers. The databases Medline Complete and SCOPUS were used, where 82 and 370 studies were identified, respectively. From these identified studies, 44 studies were removed due to being duplicates. In total, 408 records were screened. Out of these records, 364 records were excluded due to being irrelevant to the topic. 44 registers were sought for retrieval, of which 6 reports were not retrieved. 38 reports were assessed for eligibility, of which 22 were excluded due to not providing relative risk, 6 were excluded due to not being in humans, and 3 were excluded for not including the common variables. Finally, 7 studies were included in this review.

In ***Table 1,*** the primary characteristics of the included studies were demonstrated. This systematic review includes 7 studies. Of these 7 studies, 2 were case-control studies and 5 were randomized controlled trials. 2 of the 7 studies were conducted in the USA, 2 further studies in Brazil, 1 study in Taiwan, 1 study in Spain, and 1 study in Chile. The total amount of participants in this study is 958,837 women. On average, the gestation period of all the studies was between 6-24 weeks and the age was between 16-40 years

Table 1: *Characteristics of Included Studies*

Author/Year/ Country	Type of Study	Sample Size (n = number of participants)	Sample Characteristics	Definition of Periodontal Disease	Aim of the Study	Conclusions
Chen et al., 2022, Taiwan (7)	Case-Control Study	n = 869,580 (non-LBW) n = 86,958 (LBW)	Age ≥ 18 years		Whether regular scaling performed prior to pregnancy improves the risk of APOs	PD is an important risk factor for preterm LBW newborns
Caneiro-Queija et al. 2019, Spain (8)	Randomized Clinical Trial	n = 40 (total) n = 20 (test group) n = 20 (control group)	Age 18-40 years < 24 weeks of gestation		Analyze if non-surgical treatment of PD can reduce APOs	Non-surgical periodontal treatment did not reduce the risk of APOs

Oliveira et al., 2010, Brazil (9)	Case-Control Study	n = 246 (total) n = 122 (non-surgical treatment during gestation) n = 124 (no treatment during gestation)	Age 18-35 years 12-20 weeks of pregnancy	Presence of four or more teeth with one or more sites with PD ≥ 4 mm and CAL ≥ 3 m	Effects of non-surgical periodontal treatment in the occurrence of APOs	Non-surgical periodontal treatment did not reduce the risk for PL or LBW
López et al., 2002, Chile (10)	Randomized Controlled Trial	n = 400 (total) n = 200 (periodontal treatment before 28 weeks of gestation) n = 200 (periodontal treatment after delivery)	Age 18-35 years 9-21 weeks of gestation	Presence of 4 or more teeth with 1 or more sites with PD ≥4 mm and with clinical attachment loss ≥3 mm at the same site	Evaluate the association between PD and PLBW	PD appears to be a risk factor for PLBW
Sant'Ana et al., 2010, Brazil (11)	Controlled Clinical Trial	n = 33 (total) n = 16 (intervention group) n = 17 (no intervention group)	Age 16-39 years old 9-24 weeks of gestation		Evaluate the effects of non-surgical treatment of PD on APOs	Periodontal treatment was associated to a decreased risk of APOs

Macones, MD et al., 2010, USA (12)	Randomized Clinical Trial	n = 757 (total) n = 378 (active group) n = 379 (control group)	Age 24.1 ± 5.2 years old (active group) Age 24.4 ± 5.7 years old (control group) 6-20 weeks of gestation	Attachment loss ≥3 mm on ≥3 teeth Moderate/Severe: Attachment loss of ≥ 5 mm on ≥ 3 teeth	Whether treating PD in pregnancy will reduce the incidence of SPTD	Treating PD does not reduce the incidence of SPTD
Michalowicz, D.D.S. et al., 2006, USA (13)	Randomized Controlled Trial	n = 823 (total) n = 413 (treatment group) n = 410 (control group)	13-17 weeks of gestation	4 or more teeth with a probing depth of at least 4 mm and a clinical attachment loss of at least 2 mm, as well as bleeding on probing at 35% or more of tooth sites	Effect of non-surgical periodontal treatment on preterm birth	Treatment of PD does not significantly alter rates PB or LBW

In ***Table 2,*** the author, year, and country of each study is listed. Furthermore, the sample size and sample characteristics, which include the age and the weeks of gestation, if available. The total sample size of the selected studies for this objective is 956,938 participants. Chen et al. (7) had a large sample size with 956,538 participants overall.

Table 2: *Measurement of risk of APOs due to PD during pregnancy*

Author	Year	Country	Sample Size (n = number of participants)	Sample Characteristics	Definition of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Spontaneous Preterm Delivery (SPTD)	Relative risk (RR) (95% CI) of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Preterm/Low Birth Weight (PLBW)
Chen et al. (7)	2022	Taiwan	n = 869,580 (non-LBW) n = 86,958 (LBW)	Age ≥ 18 years	PL: <37 weeks of gestation LBW: <2,500 g	LBW: 0.93 (0.91-0.94) p <0.001
López et al. (10)	2002	Chile	n = 400 (total) n = 200 (periodontal treatment before 28 weeks of gestation) n = 200 (periodontal treatment after delivery)	Age 18-35 years 9-21 weeks of gestation	PL: < 37 weeks LBW: < 2,500 g	PL: 5.48 (1.17-27.71) p = 0.014 LBW: 6.26 (0.73-53.78) p = 0.052 PLBW: 5.49 (1.65-18.22) p = 0.001

Table 3 analyzes the results of whether treatment of periodontal disease has an influence on the risk of APOs. 5 out of 7 studies did not find that treatment of PD altered or decreased the risk or rates of PB and/or LBW. The studies were published between 2006 to 2019. The studies were published between 2006 to 2019. 1 study was realized in Spain, 2 studies in Brazil, and 2 studies were conducted in the USA. The total number of sample size between all the studies is 1,899 participants.

Table 3: Measurement of risk whether periodontal treatment is associated to APOs

Author	Year	Country	Sample Size (n = number of participants)	Sample Characteristics	Definition of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Spontaneous Preterm Delivery (SPTD)	Relative risk (RR) (95% CI) of Preterm Labor (PL) and/or Low Birth Weight (LBW) and/or Preterm/Low Birth Weight (PLBW)
Caneiro-Queija et al. (8)	2019	Spain	n = 40 (total) n = 20 (test group) n = 20 (control group)	Age 18-40 years < 24 weeks of gestation	PL: <37 weeks of gestation LBW: <2,500 g	PL: 0.28 (0.02-2.98) LBW: 0.28 (0.02-2.98)
Oliveira et al. (9)	2010	Brazil	n = 246 (total) n = 122 (non-	Age 18-35 years 12-20 weeks of pregnancy	PL: <37 weeks of gestation LBW: < 2,500 g	PL: 0.915 (0.561-1.1493) LBW: 0.735

			surgical treatment			(0.459-1.179)
Sant'Ana et al. (11)	2010	Brazil	n = 33 (total) n = 16 (intervention group) n = 17 (no intervention group)	Age 16-39 years old 9-24 weeks of gestation	PL: < 37 weeks LBW: <2,500 g	PLBW: 7.58 (1.07-53.59) p = 0.02
Macones, MD et al. (12)	2010	USA	n = 757 (total) n = 378 (active group) n = 379 (control group)	Age 24.1 ± 5.2 years old (active group) Age 24.4 ± 5.7 years old (control group) 6-20 weeks of gestation	SPTD: ≤ 35 weeks LBW: 2,500 g PL: < 35 weeks	PL: 1.61 (0.90-2.88) p = 0.11 LBW: 1.38 (0.92-2.08)
Michalowicz, D.D.S. et al. (13)	2006	USA	n = 823 (total) n = 413 (treatment group) n = 410 (control group)	13-17 weeks of gestation	PL: < 37 weeks LBW: < 2,500 g	Treatment group vs. control group: 0.93 (0.63-1.37) p = 0.70

DISCUSSION

These adverse pregnancy outcomes may include preterm labor, low birth weight, preeclampsia, and more. Due to the differences between the findings of the studies, it is necessary to fulfill more studies and gather additional evidence to prove the direct relationship between periodontal disease during pregnancy, the treatment of it, and how it may affect pregnancy outcomes.

It can be said that the authors Chen et al. (7) have clearly proven, through their findings, that periodontal disease during pregnancy is an important risk factor for preterm low birth weight newborns. The relative risk of low birth weight was 0.93 in a 95% confidence interval of 0.91-0.94. The findings of this study have proven that the risk of adverse pregnancy outcomes, specifically low birth weight, significantly increased in women who underwent periodontal treatment, making periodontal disease a risk factor for low-birth-weight newborns.

On the other hand, in the study conducted by authors Caneiro-Queija et al. (8), non-surgical periodontal treatment did not reduce the risk of adverse pregnancy outcomes, such as preterm birth and/or low-birthweigh.

Ultimately, Caneiro-Queija et al. (8) did not observe any significant differences for the variables preterm birth and/or low-birthweight of their study. Oliveira et al. (9) and Michalowicz et al. (13) also supported this finding in the results of their studies. These authors have established that the treatment of periodontitis in pregnant women is safe, however, it did not reduce the incidence of premature labor and/or low birthweight.

However, the authors López et al. (10) have stated that periodontal disease appears to be a risk factor for PLBW. The authors Sant'Ana et al. (11) have stated that periodontal treatment was associated to a decreased risk of adverse pregnancy outcomes. Moreover, the randomized clinical trial published by authors Macones et al. (12) concluded that treating periodontal disease does not reduce the incidence of spontaneous preterm delivery. Like the authors Macones et al. (12) have mentioned, the authors Michalowicz et al. (13) have detailed that the treatment of periodontal disease does not significantly alter rates of preterm birth or low birth weight.

In the systematic review by authors Teshome et al. (14), similar results have been found regarding the relationship between periodontal disease and preterm low birth weight (14). Limitations of this systematic review include the inconsistencies between the definitions of periodontal disease among the various included studies. Apart from the differences among the definitions, 3 studies did not include any definition of periodontal disease. Another limitation of this systematic review is the discrepancy between sample sizes across the included studies. Some studies have proportionally smaller sample sizes than other studies. In conclusion, it can be said that:

- The association between periodontal disease and pregnancy has been proven by various studies, however, more studies are necessary to confirm this relationship due to the discrepancy between the results of the included studies.

- This systematic review has shown that periodontal disease can be considered a risk factor for adverse pregnancy outcomes, such as preterm birth and/or low birth weight.
- The presented evidence does not consequently verify whether treatment of periodontal disease in pregnant women could prevent adverse outcomes of pregnancy. More studies are needed to support this claim.

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ANNEX

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

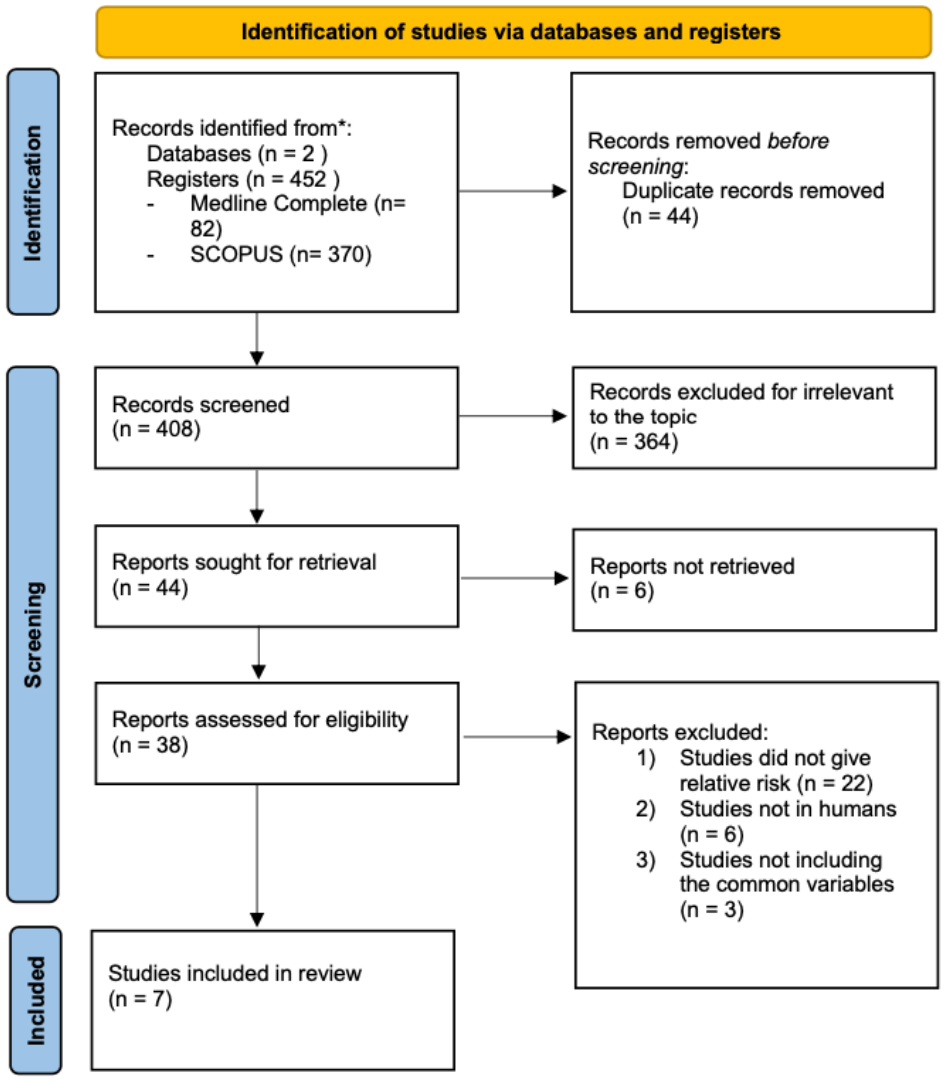

Figure 1. PRISMA flowchart of searching and selection process of articles