Al-Farabi Kazakh National University

UCD: 616.31:618.2(043) On manuscript right

**ORALKHAN ZHIBEK**

# Oral health status and adverse pregnancy outcomes

8D10102 - Medicine

Dissertation for the degree of
doctor of Philosophy (PhD)

Domestic scientific supervisor
Candidate of Medical Sciences,
Associate Professor Zhurabekova Gulmira
Foreign scientific supervisor
PhD,MD
Professor Guang Wang

Republic of Kazakhstan
Almaty, 2026

**CONTENTS**

## NORMATIVE REFERENCES

This dissertation is written and formatted in accordance with the following standards:

GOST 7.32-2001 System of standards for information, librarianship and publishing. Research report. Structure and rules of registration.

GOST 7.1–2003 Bibliographic record. Bibliographic description. General requirements and rules of compilation.

GOST 7.1-84 System of standards for information, librarianship and publishing. Bibliographic description of the document. General requirements and rules for compilation.

GOST 7.9-95 (ISO 214-76) System of standards for information, librarianship and publishing. Abstract and abstract. General requirements.

GOST 7.12-93 System of standards for information, library and publishing business. Bibliographic record. Abbreviation of words in Russian. General requirements and rules.

GOST 15.101–98 System for the development and production of products. The procedure for performing research work.

GOST R ISO 14155–2014 Clinical investigation of medical devices for human subjects – Good clinical practice.

GOST R ISO 15189–2008 Medical laboratories – Requirements for quality and competence.

Declaration of Helsinki (WMA, 2013) Ethical Principles for Medical Research Involving Human Subjects.

SanPiN 3.01.007.99 Hygienic requirements for the provision of dental services in the Republic of Kazakhstan.

## DEFINATIONS

In the present dissertation, the following terms with corresponding definitions are used:

**Adverse pregnancy outcomes** – refers to any unfavorable or harmful event occurring during pregnancy, labor, or the postpartum period that negatively affects the health of the mother, the fetus, or the newborn.

**Preterm birth –** is defined as the delivery of a live-born infant before 37 completed weeks of gestation or less than 259 days from the first day of the last menstrual period.

**Extremely Preterm Birth** –is defined as a live birth that occurs before 28 completed weeks of gestation – that is, less than 28 weeks (0–27 weeks + 6 days) of pregnancy.

**Very Preterm Birth** – is defined as a live birth occurring from 28 weeks to less than 32 completed weeks of gestation — that is, between 28 weeks 0 days and 31 weeks 6 days.

**Moderate to Late Preterm Birth** – refers to a live birth occurring between 32 weeks 0 days and 36 weeks 6 days of gestation.

**Periodontitis** – is a chronic inflammatory disease of the supporting structures of the teeth (the gingiva, periodontal ligament, cementum, and alveolar bone) that results in progressive destruction of connective tissue attachment and alveolar bone, ultimately leading to tooth mobility and loss if untreated.

**Bleeding on probing** – is defined as the presence of bleeding from the gingival sulcus or pocket within 10–15 seconds after gentle probing of the gingival margin using a calibrated periodontal probe (applied force ≈ 0.25 N).

**Probing depth** – is the measured distance in millimeters from the gingival margin to the bottom of the gingival sulcus or periodontal pocket using a calibrated periodontal probe with gentle force (~0.25 N).

**Clinical attachment loss** – is the distance from the cementoenamel junction (CEJ) to the base of the gingival sulcus or periodontal pocket, measured in millimeters using a periodontal probe.

**Decayed, Missing, and Filled Teeth Index** – is a quantitative measure of dental caries experience in permanent teeth. It represents the total number of teeth in an individual that are: D – Decayed (carious, untreated), M – Missing (extracted due to caries), or F – Filled (restored due to caries). DMFT = D + M + F

**SHapley Additive exPlanations** – is a modern, mathematically grounded method for interpreting complex machine learning models — especially useful in your dissertation's stacking multiclass model for preterm birth prediction.

## ABBREVIATIONS AND ACRONYMS

| | | |
|---|---|---|
| APOs | – | Adverse pregnancy outcomes |
| PTB | – | Preterm birth |
| EPTB | – | Extremely Preterm Birth (less than 28 weeks) |
| VPTB | – | Very Preterm Birth (28–31 weeks) |
| MLPTB | – | Moderate to Late Preterm Birth (32–36 weeks) |
| OHRQoL | – | Oral Health-Related Quality of Life |
| WHO | – | World Health Organization |
| BOP | – | Bleeding on probing |
| PD | – | Probing depth |
| CAL | – | Clinical attachment loss |
| DMFT | – | Decayed, Missing, and Filled Teeth Index |
| SB | – | Sigle blind |
| DB | – | Duble blind |
| F. nucleatum | – | Fusobacterium nucleatum |
| qPCR | – | Quantitative Polymerase Chain Reaction |
| SPSS | – | Statistical Package for the Social Sciences |
| SHAP | – | SHapley Additive exPlanations (used in machine learning model interpretation) |
| ANOVA | – | Analysis of Variance |
| OR | – | Odds Ratio |
| PRISMA | – | Preferred Reporting Items for Systematic Reviews and Meta-Analyses. |
| ANC | – | Antenatal Care |
| LMICs | – | low- and middle-income countries |
| GDM | – | Gestational diabetes mellitus |
| SDGs | – | Sustainable Development Goals |

# INTRODUCTION

## Relevance of the research

A society's health and its prospects have long been seen as key measures of its level of civilization. Key indicators of population health include physical development, birth rate, morbidity, and mortality [1-2]. Therefore, to predict and improve the health of future generations, it is necessary to conduct in-depth studies and develop effective measures to reduce perinatal morbidity and mortality, while accounting for all contemporary adverse factors. The study of the relationship between oral health and adverse pregnancy outcomes is an important area of contemporary biomedical research. It aligns with the Sustainable Development Goals (SDGs) No. 3, "Good Health and Well-being," and No. 10," Reduced Inequalities." From a public health perspective, adverse pregnancy outcomes (APOs) – such as preterm birth (PTB), low birth weight, and preeclampsia – remain significant challenges that significantly contribute to high perinatal morbidity and mortality worldwide [3].

Adverse pregnancy outcomes (APOs) are defined as complications during pregnancy that negatively affect the health of the mother and fetus [1,p. 3]. Among these, preterm birth (PTB) is the most extensively studied and intractable complication, associated with high perinatal mortality and morbidity [4]. The World Health Organization (WHO) has identified PTB as one of the "top ten" global research priorities through 2025 [5-6]. Furthermore, the United Nations considers research on PTB central to achieving reductions in neonatal mortality and the Sustainable Development Goals by 2030 [7].

Preterm-born infants face not only a higher risk of death and health complications but also may suffer chronic health problems [1,p. 3]. PTB is responsible for approximately one in ten cases of childhood hearing impairment, one in five cases of intellectual disability, one in three cases of visual impairment, and nearly half of all cases of cerebral palsy [8]. In the long term, individuals born prematurely have an increased risk of neurological disorders [9,10], delayed language development [11], reduced cognitive function [12], and chronic diseases such as diabetes [13], cardiovascular disorders [14-15], and certain cancers [16]. Mothers who deliver preterm are also at higher risk of recurrent preterm delivery [17]. Advances in neonatal care, including antenatal corticosteroids, surfactant therapy, and kangaroo mother care, have significantly improved survival and long-term outcomes for preterm infants [18-19].

Nevertheless, the burden of PTB remains substantial, particularly in regions with limited access to high-quality perinatal care, underlining the importance of primary prevention. Thus, preventing PTB is essential to improving perinatal health outcomes and reducing infant mortality. In addition to its health implications, PTB imposes a significant financial burden on healthcare systems and families, leading to social, psychological, and economic consequences both globally and in Kazakhstan [20-21]. Therefore, preterm birth should be regarded not only as a medical but also as a societal issue of national importance. Global health organizations such as the March of Dimes

and the International Federation of Gynecology and Obstetrics (FIGO) emphasize the need to move beyond traditional clinical and preventive strategies by expanding research to develop innovative interventions for PTB [22-23]. Extensive studies have identified maternal, environmental, psychological, social, and genetic factors as key contributors to preterm birth [24]. In response, global consensus guidelines and intervention frameworks have been established for identifying and managing high-risk pregnancies [25]. Preventive strategies include strengthening antenatal care systems, screening and managing infections such as periodontal disease, providing nutritional supplementation, and promoting behavioral education among pregnant women [26].

The oral cavity is a complex ecosystem, and periodontal disease is a potential source of systemic inflammation [27]. Systemic inflammation, even in the absence of direct infection, can impair placental function by disrupting trophoblast invasion and spiral artery remodeling through cytokine-mediated mechanisms and by inducing oxidative stress [28]. These processes compromise maternal–fetal tolerance and can lead to premature rupture of membranes and spontaneous labor [29-30]. Another proposed mechanism involves the hematogenous dissemination of oral pathogens to the fetal–placental unit [31-32]. Among these microorganisms, *Fusobacterium nucleatum* is a well-recognized keystone pathogen in periodontal disease and has been frequently identified in placental and amniotic tissues in cases of spontaneous preterm labor [33-34]. Its ability to adhere to host cells, evade immune responses, and penetrate endothelial barriers underscores its role as a plausible biological mediator in the oral–systemic disease axis [35].

It should be noted that, as preterm births continue to account for a substantial proportion of infant mortality in Kazakhstan [36], identifying and investigating specific biological and behavioral markers associated with oral health is increasingly important. Research aimed at elucidating the role of oral inflammation and periodontal pathogens in pregnancy complications has significant potential to improve diagnostic and preventive strategies. Assessing oral health status, particularly periodontal disease, may serve as a valuable biomarker of maternal and fetal well-being, enabling early identification of women at risk of preterm birth [37]. Incorporating such oral health indicators into routine prenatal screening could substantially simplify risk assessment, reduce reliance on invasive and costly laboratory procedures, and improve maternal and neonatal outcomes through timely and targeted preventive measures [38]. Moreover, promoting oral health is a low-cost, accessible, and scalable public health intervention—particularly beneficial in resource-limited settings where preterm birth rates remain high [38,p. 685].

**Object of the study**

Pregnant women who participated in the prospective cohort and case–control components of the research.

**The purpose of the study**

To investigate whether oral diseases contribute to the etiology of preterm birth by examining their interaction with socioeconomic and maternal factors, and to elucidate the underlying mechanisms through assessment of Fusobacterium nucleatum in saliva and placenta.

**Objectives of the study**

1. To conduct a systematic review and meta-analysis of international and national research data to determine the strength and consistency of the association between oral diseases and preterm birth.

2. To identify and analyze maternal risk factors contributing to preterm birth, including socioeconomic, behavioral, and clinical determinants, and self-reported oral symptoms, based on data obtained from a prospective pregnancy cohort in the Republic of Kazakhstan.

3. To determine the individual and combined effects of oral diseases and maternal risk factors on spontaneous preterm birth in a case–control sample, and to explore potential biological mechanisms by assessing periodontal status, behavioral determinants, and the presence of Fusobacterium nucleatum in placental tissue.

**Scientific novelty of the study**

The present study is the first in Kazakhstan to systematically investigate the contribution of maternal oral disease to preterm birth, integrating socioeconomic, clinical, and molecular data. Assessing Fusobacterium nucleatum in saliva and placental tissues provides novel mechanistic insights into oral–placental interactions. Additionally, the study uses a stacked multiclass machine learning model to analyze complex interactions among biological, behavioral, and environmental risk factors, enabling the identification of early predictors of preterm birth in the regional population. This integrated, data-driven approach bridges global evidence with local health realities, informing future prevention strategies.

**The practical significance of the study**

This study has substantial practical relevance, providing evidence-based guidance to inform targeted interventions that reduce the risk of preterm birth (PTB) by incorporating maternal oral health management as an integral component of prenatal care. The identification of key social, clinical, and behavioral predictors of PTB – including low maternal education, prior preterm birth, and periodontal disease – enables the development of risk stratification frameworks for early detection and individualized prenatal care.

The demonstration of a significant association between periodontitis and preterm delivery underscores the role of maternal periodontal health as a modifiable risk factor, highlighting the need to incorporate routine oral health screening and preventive measures into standard prenatal care protocols. By evaluating the interaction of socioeconomic, lifestyle, and clinical variables, the study supports a holistic, interdisciplinary approach to maternal health, emphasizing the integration of dental, obstetric, and public health services.

**Provisions submitted for defense**

1. A systematic review and meta-analysis demonstrated a significant association between maternal periodontitis and increased risk of preterm birth, based on both international and local datasets.

2. In the cohort study, maternal periodontal status was identified as a significant predictor of spontaneous preterm birth, with stronger associations observed among women of lower socioeconomic status.

3. Advanced analytical approaches, including machine learning models, were applied to integrate clinical, socioeconomic, and microbiological data, enabling accurate prediction of preterm birth risk. These models provide a framework for individualized risk stratification, supporting early identification of high-risk pregnancies and informing targeted intervention strategies.

4. Based on these findings, practical, evidence-based recommendations has been formulated to support the inclusion oral health care into routine prenatal practice. These include structured oral health education programs for pregnant women, early periodontal screening, timely diagnosis, proper oral hygiene practices, and appropriate treatment during pregnancy. Enhancing awareness and knowledge can improve health-seeking behaviors, reduce the burden of maternal oral infections, and consequently lower the incidence of preterm birth, thereby improving both maternal and neonatal health outcomes.

**Relation to the Plan of Major Scientific Works**

The study was conducted within the framework of the project "Clinical, Genomic and Environmental Variable Approach to Preterm birth" funded by the Ministry of Science and Higher Education of the Republic of Kazakhstan. State registration number AP14869249. The research was carried out under the supervision of Associated Professor Zhurabekova G.A.

**Approval of the work**

The main content of the dissertation has been published in international and local scientific journals and discussed at conferences. Three of which appeared in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan, while three were published in foreign periodicals: one in a journal «BMC pregnancy and childbirth» indexed in the scopus database (Q1); one in journal «Iranian Journal of Medical Sciences» indexed in the scopus database (Q2); one in a journal Human ecology» indexed in the scopus database (Q3); Four abstracts in the proceedings of international conferences.

**The doctoral candidate's personal contributions** included collecting data on the research topic; conducting primary theoretical and experimental studies, including analysis, interpretation, and presentation of results; preparing manuscripts for publication; and writing the dissertation.

**Scope and structure of the dissertation**

Volume and Structure of the Dissertation. The dissertation comprises 129 pages and is organized into sections, including abbreviations and notations, introduction, literature review, materials and methods, results, conclusion, practical recommendations, and a reference list of 415 sources. The dissertation contains 16 tables, 19 figures, and 1 appendix.

# 1 LITERATURE REVIEW

## 1.1 Conceptual and Epidemiological Framework of Preterm Birth

Adverse pregnancy outcomes (APOs) describes several pregnancy related complications that affect the health of mother, fetus, or both [1,p. 3]. The APOs include: spontaneous abortion (miscarriage), ectopic pregnancy, stillbirth, gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (preeclampsia), preterm birth, and low birth weight [2,p. 3]. The most severe adverse outcome of pregnancy is loss of life. Maternal death has become an infrequent event, with many countries reporting maternal mortality ratios of 5–10 per 100,000 live births [5,p. 1261]. Disparities in infant deaths are not quite as wide but remain substantial, ranging from 4–5 to 100 per 1000 live births [5,p. 1261]. Even in survival, the mother and child may face severe maternal or infant morbidity throughout their lives [5,p. 1261]. The most commonly studied of these proxies has been preterm birth and low birth weight, based on proxy outcomes for death and diseases[2,p. 12], which were identified as a "top ten" research priority to 2025 by the World Health Organization [4,p. 37]. The United Nations has also positioned PTB research as central to achieving reductions in newborn deaths and the Sustainable Development Goals by 2030 [5,p. 1261].

Worldwide research has emphasized early identification and risk prediction as central strategies for PTB prevention [23,p. 13], involving clinical interventions, public health improvement and behavioral modifications. For example, evidence-based clinical interventions include cervical cerclage for women with short cervical length, progesterone therapy, and treatment of maternal infections [25,p. 12505]. Midwife-led continuity of care and routine prenatal monitoring have also been shown to reduce PTB rates by facilitating timely identification and management of complications [26,p. 172]. Systematic reviews and meta-analyses have demonstrated that integrating clinical and sociodemographic risk factors improves early stratification of high-risk pregnancies [20,p. 50]. Despite these advances, models suggest that implementing currently recommended interventions could reduce preterm birth rates by only 5–10% in many settings, underscoring the need for novel strategies and context-specific approaches [39-40].

The etiology of PTB is multifactorial, involving biological, social, environmental, and behavioral factors. Maternal infections and systemic inflammation have been increasingly recognized as essential contributors, with evidence suggesting that oral health—particularly periodontitis—may play a causal role through microbial translocation and inflammatory pathways [27,p. 769]. Socioeconomic determinants, including maternal education, income, and access to healthcare, interact with clinical risk factors, further modifying PTB risk. Emerging research also highlights the role of the maternal microbiome, genetic predisposition, and environmental exposures as potential mechanistic contributors. However, these factors remain underexplored in many low- and middle-income countries (LMICs) [33,p. 103].

### 1.1.1 Definition and classification of preterm birth

Preterm birth (PTB) is defined as any live birth before 37 completed weeks of gestation [1,p. 15]. According to the World Health Organization (WHO), gestational age should always be reported in complated weeks; therefore, an infant born at 36 weeks and 6 days is classified as 36 weeks, not 37 weeks [26,p. 172]. This convention is essential for distinguishing between PTB and LBW children. Because the exact timing of conception is often difficult to determine—particularly in natural, unassisted conceptions—earlier medical practice relied on birth weight rather than gestational age as a proxy for maturity [1, p. 15].

Clinically, PTB is now recognized as a heterogeneous syndrome. Approximately 40–45% of preterm deliveries result from idiopathic spontaneous preterm labor, 25–30% from preterm premature rupture of membranes (PPROM), and 30–35% are medically indicated due to maternal or fetal complications [1,p. 15]. Gestational-age subgroups are widely used because delivery timing strongly predicts neonatal outcomes [23, p.13]. Preterm birth is commonly classified according to gestational age as extremely preterm (EPTB) with less than 28 weeks of gestation, very preterm (VPTB) with 28 to less than 32 weeks of gestation, moderate to late preterm (MLPTB) with 32 to less than 37 weeks of gestation [23,p. 13].

These subcategories reflect the broad spectrum of etiologic pathways and different neonatal outcomes. Evidence shows that extremely and very preterm births are more strongly associated with severe maternal conditions such as intrauterine infection, chorioamnionitis, placental insufficiency, short cervical length, previous preterm birth, multiple prior miscarriages, and high inflammatory burden [29,p. 56]. By contrast, moderate-to-late preterm births are more frequently linked to maternal hypertensive disorders, gestational diabetes, anemia, obesity, inadequate antenatal care, and medically indicated early delivery [20,p. 50]. Socioeconomic determinants—including maternal education, housing stability, access to healthcare, and psychosocial stress consistently increase the risk of MLPTB, partly through chronic stress pathways, which affect the immune regulation [41-42]. Behavioral factors such as maternal smoking, alcohol use, poor diet quality, and periodontal disease are also more strongly associated with late preterm birth but may contribute to infection-mediated early PTB through inflammatory mechanisms [37,p. 182]. Given these heterogeneous determinants, classifying by gestational age enables more precise identification of risk factors specific to each group.

### 1.1.2 Epidemiology of preterm birth

Recent global estimates indicate that on the order of 10–11% of all live births are preterm (roughly 13–15 million babies per year), and complications of prematurity account for a significant fraction of neonatal and under-5 deaths worldwide [7,p. 9]. Global evidence (2010–2020) has underscored substantial geographic variation: the highest absolute burdens are in sub-Saharan Africa and southern Asia, while middle- and high-income countries show wide heterogeneity driven by differences in obstetric practice, demographic structure, and data quality [4, p. 37]. Trend analyses also show that, in many settings with reliable data, preterm rates have changed little or have increased over recent decades, underscoring gaps in prevention [22, p. 5].

Across Central Asia, PTB remains a significant contributor to neonatal morbidity and mortality, with substantial variation in prevalence among countries. According to the UNICEF/WHO Estimates (2023) and the Global Burden of Disease (GBD) 2021 data, PTB rates in Central Asian states generally range from 6% to 10% [7,p. 6], reflecting moderate to high levels relative to global averages. Reliable, country-level estimates of preterm birth (PTB) for Uzbekistan are limited. The Lancet Global Health country estimates [4,p. 37] provide the most widely cited country-level figures. According to that source, the estimated numbers of preterm births in 2014 were: Uzbekistan-69,800; Tajikistan-26,400; Kazakhstan-19,700; Kyrgyzstan-16,100; and Turkmenistan-11,600. Kyrgyzstan and Uzbekistan report some of the highest national rates in the region, with PTB accounting for nearly one-third of neonatal deaths. At the same time, Turkmenistan and Tajikistan reported less optimistic data [7, p.]. 6]. The majority of preterm deliveries in Central Asia are reported in urban areas, where limited neonatal care capacity and access to care remain significant constraints to survival [18,p. 6].

The previous findings, along with data from Several multicountry analyses conducted in collaboration with the WHO Regional Office for Europe and the United Nations Population Fund, have also emphasized persistent inequalities in maternal health services across Central Asia, particularly in rural areas, where early detection and management of high-risk pregnancies are often delayed [7,p. 6]. Case–control studies from Kyrgyzstan and Uzbekistan have identified maternal infection, anemia, poor nutrition, and low socioeconomic status as the most common predictors of PTB, consistent with global evidence [43-45]. However, overall, while regional public health initiatives have contributed to gradual declines in infant mortality over the past decade, preterm birth continues to represent one of the leading causes of neonatal loss in Central Asia [20,p. 50]. The limited scope of epidemiological and mechanistic studies underscores the need for coordinated multicenter research to better understand the biological and social determinants of PTB in the Central Asian context [23,p. 13].

Kazakhstan, a Central Asian country, reports approximately 400,000 infant deliveries annually, with a preterm birth (PTB) rate of around 4.7%, placing it among the nations with the lowest PTB rates globally [21,p. 1682]. Despite this relatively favorable indicator, Kazakhstan's infant mortality rate (IMR) was 8.7 deaths per 1,000 live births in 2022, reflecting steady progress relative to previous years but underscoring ongoing public health challenges [36,p. 923]. Prematurity contributes to approximately 1% of infant deaths, which highlights the significant vulnerability of preterm infants to severe health complications [22,p. 7].

National and regional data, however, reveal notable variability in reported PTB prevalence across data sources and clinical settings. Routine national statistics typically report rates of 5–7%, whereas specialized neonatal and obstetric care centers—particularly those managing high-risk pregnancies—document substantially higher rates, reaching up to 15% in some institutions [21, p. 1682]. This variation reflects both true regional heterogeneity and differences in case ascertainment and reporting practices.

Marked regional disparities further compound the national burden. The Atyrau, Almaty, and Aktobe regions consistently report higher rates of infant mortality than the national average [36, p. 923]. Specialized neonatal centers in these regions manage hundreds of premature infants annually, including extremely low birth weight cases of approximately 400 grams, requiring advanced intensive care for survival. Despite these medical advances, approximately 18 out of every 1,000 children die annually, emphasizing persistent challenges in reducing infant and neonatal mortality across the country [21, p. 1682].

Although progress has been made, the regional evidence base in Kazakhstan remains limited in both scale and methodological depth compared with research from high-income countries. This gap underscores the need for more comprehensive, multicenter epidemiological and clinical studies to better characterize the determinants of preterm birth and to improve neonatal outcomes nationwide [20,p. 50].

### 1.1.3 Consequence of preterm birth

Preterm birth has emerged as an urgent global research priority not only because of its high prevalence but also due to the severity and lifelong nature of its consequences. Recent studies from high-income and middle-income countries consistently demonstrate that complications begin immediately after birth and persist through adulthood. Extensive neonatal cohort analyses, such as the Eunice Kennedy Shriver NICHD Neonatal Research Network study [46,47] show that extremely preterm infants (<28 weeks) experience markedly increased risks of bronchopulmonary dysplasia, necrotizing enterocolitis, severe intraventricular hemorrhage, sepsis, and long-term respiratory impairment. Similarly, the Canadian Neonatal Network cohort [48] reports that survival without significant morbidity remains below 30% among extremely preterm infants even in advanced neonatal care settings.

Long-term follow-up studies confirm that neurodevelopmental consequences extend well beyond childhood [49-52]. Recent neuroimaging research [49,p. 123] demonstrates altered cortical maturation, reduced white matter connectivity, and structural brain reorganization that persist into young adulthood. Long-term cohort follow-up by Cheong et al. [50,p. 164] further demonstrated persistent deficits in lung function and reduced exercise capacity into adolescence, while Normann et al. [51,p. 1050] identified substantially higher rates of retinopathy of prematurity and lasting visual impairment independent of birth weight. Over the past decade, neurodevelopmental and neuroimaging studies have revealed deep and enduring brain effects: Volpe [52,p. 227] described altered brain connectivity and atypical cortical maturation in preterm infants, findings supported by Twilhaar et al. [53], whose meta-analysis in JAMA Pediatrics showed that adults born preterm continue to exhibit lower IQ and academic performance even after socioeconomic adjustment. These cognitive vulnerabilities parallel the increased risks of ADHD, autism spectrum disorder, behavioral problems, and mental health disorders reported by Wolke and Johnson [54] among children and adolescents born preterm.

Preterm birth is now recognized as a lifelong condition, not confined to the neonatal period. A landmark Swedish analysis of more than four million births by Crump et al. [55] demonstrated that individuals born preterm have higher risks of early-onset hypertension, ischemic heart disease, and diabetes before age 40, findings aligned with cardiometabolic studies by Hovi et al. [56], who documented reduced insulin sensitivity and greater carotid intima–media thickness in young adults born preterm. Respiratory consequences extend into adulthood as well, as noted by Thunqvist et al. [57] linking prematurity to persistent asthma and lifelong reductions in pulmonary function.

The impacts of preterm birth extend to mothers and families. A UK cohort analysis [58] found markedly higher rates of postnatal depression, anxiety, and PTSD among mothers of preterm infants, while Bernet et al. [59] highlighted the long-term emotional and caregiving burdens associated with neurodevelopmental impairment. A 2021 systematic review [60] showed that caregiving stress, financial strain, and long-term educational support needs remain substantial for families even when infants survive without severe disability. Maternal health consequences are also significant: a Korean national study [61] demonstrated increased risks of cardiometabolic disorders and recurrent preterm birth among mothers with previous PTB. Longitudinal research by Lee et al. [62] also showed increased risks of recurrent preterm birth and postpartum metabolic disorders among mothers with a history of PTB, emphasizing multigenerational implications.

Economic analyses over the past decade underscore the substantial and persistent financial burden of prematurity. Petrou et al. [63] reported that healthcare costs remain significantly elevated for very preterm children at ages 5, 11, and 19 due to ongoing hospital admissions and long-term support needs. Russell et al. [64] identified PTB as one of the highest lifetime-cost perinatal conditions in high-income settings, while Cheah et al. [65] showed that neonatal intensive care for preterm infants places considerable strain on middle-income health systems like Kazakhstan’s.

Emerging research reveals intergenerational consequences of PTB: Laughon et al. [66] found that women born preterm are more likely to deliver preterm infants themselves, and Richards et al. [67] demonstrated that being born preterm is associated with lower educational attainment, reduced income, and decreased employment stability in adulthood. Collectively, these findings indicate that preterm birth has profound neonatal, childhood, adult, maternal, familial, economic, and intergenerational consequences—emphasizing why PTB prevention and mechanistic research remain global priorities.

### 1.2 Risk Factors of Preterm Birth

Despite advancements in maternal and neonatal care, the complexities underlying preterm birth continue to perplex researchers and clinicians alike [5,p. 1261]. Worldwide research has emphasized early identification and risk prediction as central strategies for PTB prevention, whereas PTB's multifactorial nature arises from a complex interplay of biological, environmental, and socioeconomic determinants [18,p. 3].

A robust body of international research indicates that early detection of high-risk pregnancies—through the assessment of maternal infections, inflammation, cervical insufficiency, metabolic and vascular disorders—facilitates timely therapeutic measures such as progesterone supplementation, cervical cerclage, and infection control, all of which have been shown to mitigate PTB risk [15,p. 2828]. Moreover, delineating modifiable risk factors, including periodontal disease, inadequate antenatal care, psychosocial stress, tobacco use, and nutritional deficiencies, is particularly critical in low- and middle-income contexts where preventive health resources remain limited [41,p. 257]. Contemporary predictive models that integrate clinical, microbiological, and genetic markers have further enhanced the capacity for individualized risk assessment, supporting precision-based approaches to maternal care [24,p. 494]. Consequently, a systematic investigation of PTB determinants is not only of academic and clinical relevance but also aligns with global public health priorities aimed at reducing neonatal mortality and achieving the Sustainable Development Goals [32,p. 30].

### 1.2.1 Maternal factors

Maternal factors encompass a broad range of biological, physiological, behavioral, and reproductive characteristics that play a central role in shaping pregnancy outcomes and determining the likelihood of preterm birth [27,p. 769]. These factors reflect both intrinsic maternal conditions—such as age, anthropometric traits, genetics, and obstetric history—as well as pregnancy-specific adaptations involving the cardiovascular, endocrine, and immune systems [24,p. 494]. Maternal factors influence pregnancy through multiple pathways, including placental development, uterine contractility, cervical remodeling, hormonal regulation, and the maternal inflammatory response, all of which are critical for maintaining gestational length [29,p. 56]. Variations in maternal health status—whether related to pre-existing medical conditions, nutritional reserves, immune function, or prior reproductive experiences—can disrupt these physiological processes and increase susceptibility to early labor or preterm premature rupture of membranes [15,p. 2828]. Understanding maternal factors is therefore essential for identifying women at elevated risk, guiding clinical monitoring, informing preventive interventions, and improving both maternal and neonatal outcomes [17,p. 15402].

#### 1.2.1.1 Maternal demographic factors

Numerous studies have highlighted the influence of maternal characteristics on the risk of premature birth [24,p. 494]. Factors such as maternal age, particularly younger than 20 years or older than 40 years, short maternal stature (<150 cm), excessive thinness, and obesity during pregnancy are all associated with a heightened likelihood of preterm delivery [1,p. 3]. Contemporary evidence from a large U.S. population-based cohort by Rosenberg et al. [68] further underscores the impact of maternal body mass index (BMI) on prematurity. Their findings confirm a U-shaped association, with underweight women experiencing higher rates of spontaneous preterm birth and obese women exhibiting increased medically indicated preterm birth

due to pregnancy complications [68,p. 419]. Additional evidence from Scandinavian population registries—such as the Swedish Medical Birth Register and the Danish National Birth Cohort—confirms a U-shaped relationship between BMI and PTB risk, with underweight women exhibiting higher rates of spontaneous PTB and obese women experiencing increased medically indicated PTB due to pregnancy complications [69,70]. Similar patterns have been observed in Asian populations: a Japanese cohort study involving more than 90,000 pregnancies reported that maternal height below 150 cm and BMI <18.5 were independently associated with early PTB [71]. In contrast, a multicenter Chinese study demonstrated that women with BMI ≥30 had significantly higher odds of both early and late PTB [72].

These findings suggest that both undernutrition and overnutrition during pregnancy can disrupt optimal fetal development and increase the likelihood of preterm delivery [71,p. 168]. Young or advanced maternal age and shorter maternal stature may also contribute due to physiological limitations or underlying health complications. Therefore, monitoring maternal nutritional status and ensuring proper care for women at these extremes of risk are essential strategies for reducing the incidence of preterm birth and improving overall pregnancy outcomes [26,p. 172].

#### 1.2.1.2 Maternal medical conditions

Gestational hypertension is strongly correlated with premature birth and is recognized as an independent risk factor. A retrospective analysis by Orbach et al. [73], which included 100,029 pregnant women, revealed that the likelihood of premature birth in women with hypertension during pregnancy is significantly elevated. The study showed that 22.9% of hypertensive pregnant women experienced preterm births compared to only 8.0% of healthy women, with an odds ratio (OR) of 3.69 (95% CI: 2.90–4.69). Similarly, recent large-scale epidemiological analyses have strengthened the evidence linking hypertensive disorders of pregnancy (HDP) with preterm birth. An umbrella review of 160 meta-analyses by Mitrogiannis et al. [24,p. 494] demonstrated that gestational hypertension and preeclampsia are among the strongest medical predictors of both spontaneous and medically indicated preterm birth, with pooled odds ratios frequently exceeding 3.0. Consistent findings were reported in the seminal public health review by Kramer et al. [41,p. 257], which highlighted that HDP substantially increases the risk of early iatrogenic delivery due to placental insufficiency, fetal growth restriction, and maternal complications. More recently, Harrison and Goldenberg [40,p. 556] emphasized that hypertensive disorders remain one of the leading indications for medically indicated early preterm birth worldwide, particularly before 34 weeks of gestation. Together, these contemporary data underscore the considerable impact of maternal hypertension on preterm delivery risk and highlight the importance of early detection, vigilant blood pressure monitoring, optimization of maternal cardiovascular health, and timely referral to higher-level obstetric care.

Gestational diabetes mellitus (GDM) is also recognized as a significant maternal factor associated with an elevated risk of preterm birth. Recent evidence synthesized in the extensive umbrella review by Mitrogiannis et al. [24,p. 494] confirms that

GDM—particularly when poorly controlled or accompanied by maternal obesity—significantly increases the likelihood of both spontaneous and medically indicated PTB. These findings align with earlier epidemiological analyses indicating that metabolic dysregulation, insulin resistance, and inflammation contribute to placental dysfunction and preterm delivery, particularly in high-risk populations [41,p. 257]. Global reviews by Harrison and Goldenberg [40,p. 556] and Blencowe et al. [20] further highlight GDM as a consistent contributor to medically indicated PTB due to its association with hypertensive disorders, fetal overgrowth, and iatrogenic early delivery.

Chronic maternal medical conditions also exert a substantial influence on gestational length. Large registry-based cohorts have demonstrated that women with pre-existing type 1 diabetes, chronic kidney disease, or systemic autoimmune disorders face markedly elevated risks of preterm birth, primarily due to impaired placental perfusion and systemic inflammation [55,p. 1431]. These observations are supported by mechanistic and clinical reviews showing that chronic maternal diseases can disrupt vascular, endocrine, and immunological adaptations essential for maintaining pregnancy [27,p. 769]. Collectively, these findings underscore the critical importance of optimizing maternal metabolic and chronic disease management through preconception counseling, early antenatal surveillance, and individualized care pathways to reduce the risk of PTB.

Infections are a major contributor to preterm birth, and extensive evidence indicates that maternal infection and inflammation significantly elevate the risk of early delivery. Mechanistic studies demonstrate that intrauterine inflammation—particularly chorioamnionitis and funisitis—is present in up to one-third of spontaneous preterm births before 32 weeks, underscoring its central etiologic role [29,p. 56]. Recent microbiome research has expanded this understanding. Cunnington et al. showed that disturbances in the vaginal–placental microbial continuum contribute to inflammatory activation at the maternal–fetal interface, directly increasing the likelihood of early preterm labor [74]. Similarly, Sun et al. identified significant associations between placental microbial dysbiosis and preterm birth, reinforcing the importance of infection-mediated pathways [33,p. 103]. At the same time, Cao et al. highlighted comparable effects of maternal microbiome disruption [34,p. 563].

Vaginal infections, particularly bacterial vaginosis, are closely linked to spontaneous preterm birth. A large meta-analysis by Serrano et al. demonstrated that bacterial vaginosis approximately doubles the risk of spontaneous PTB, particularly when diagnosed in early gestation [75]. These findings are consistent with earlier mechanistic work by Romero et al. showing that ascending genital tract pathogens trigger localized immune activation, cervical ripening, and early labor [29,p. 56], as well as with evidence that specific microorganisms such as Fusobacterium nucleatum can hematogenously disseminate to the placenta and induce strong inflammatory responses [31,p. 73].

Moreover, recent molecular diagnostic studies by Vulcano et al. revealed that intra-amniotic inflammation—regardless of microbial detection—substantially increases the likelihood of early preterm delivery, highlighting the role of sterile

inflammatory pathways in PTB pathogenesis [76]. Collectively, these findings emphasize the need for early identification and management of maternal infectious and inflammatory conditions to reduce inflammation-driven preterm birth.

Non-reproductive system infections also play an essential role in the pathogenesis of preterm birth, and urinary tract infections (UTIs) in particular are strongly associated with increased risk. Large population-based studies have demonstrated that asymptomatic bacteriuria and acute pyelonephritis significantly elevate the likelihood of preterm delivery. A 2020 meta-analysis of more than 30 cohort studies showed that UTIs during pregnancy increased the risk of preterm birth by approximately 70%, with the highest risk observed among women who developed pyelonephritis [77]. Recent evidence from a nationwide U.S. cohort also indicates that pyelonephritis is associated with a two- to three-fold increase in PTB risk, mediated mainly by systemic inflammation and febrile responses [78].

Systemic infections such as pneumonia similarly contribute to elevated PTB risk. A 2018 Taiwanese population-based cohort including over 1.2 million pregnancies found that community-acquired pneumonia during pregnancy increased the risk of preterm birth by nearly 60%, independent of maternal comorbidities [79]. These findings are consistent with systematic reviews demonstrating that untreated UTIs, pyelonephritis, respiratory infections, and other systemic maternal infections increase preterm birth risk through pathways involving maternal fever, hypoxia, systemic inflammation, and physiologic stress responses. Taken together, the evidence confirms that infections during pregnancy—whether intrauterine, genital tract, urinary, or systemic—substantially increase the likelihood of preterm birth and should be recognized as critical, modifiable high-risk factors requiring early detection and effective treatment.

Vaginal bleeding during pregnancy is a significant risk factor for preterm birth, and recent population-based cohorts have shown that even mild antepartum bleeding increases the likelihood of spontaneous and medically indicated preterm delivery [80]. Severe bleeding is particularly concerning, with updated analyses reporting nearly a five-fold increase in the risk of very preterm birth compared with pregnancies without bleeding episodes [41,p. 257]. Early-pregnancy bleeding, even in the absence of placenta previa or placental abruption, has also been associated with elevated risks of fetal growth restriction, placental dysfunction, and subsequent preterm delivery in recent systematic reviews [20,p. 50]. Although the mechanisms remain incompletely understood, current evidence suggests that inflammation, decidual vasculopathy, and abnormal placentation contribute to the biological pathway linking bleeding to early birth [23,p. 13].

Cervical shortening is another major predictor of spontaneous preterm birth, and contemporary guideline-based studies confirm that the risk of early delivery rises significantly when cervical length is ≤25 mm, particularly among asymptomatic high-risk women [81]. Large individual-patient meta-analyses further demonstrate that vaginal progesterone effectively reduces preterm birth rates and improves neonatal outcomes in women with a short cervix, regardless of whether they have a previous history of preterm birth [39,p. 599]. These findings have informed international

recommendations supporting targeted cervical length screening and progesterone therapy in appropriate risk groups [23,p. 13].

Polyhydramnios, characterized by excessive accumulation of amniotic fluid or elevated amniotic fluid index on ultrasound, is also associated with increased rates of preterm birth [82]. Recent prospective cohort data indicate that uterine overdistension and heightened myometrial tension significantly elevate the likelihood of uterine irritability, preterm contractions, and preterm premature rupture of membranes [81,p. 32]. In addition, large epidemiological studies report that polyhydramnios commonly coexists with maternal diabetes, fetal structural anomalies, and multiple gestation—each of which independently increases the risk of preterm delivery [20,p. 50].

Overall, maternal medical complications—including hypertensive disorders, gestational diabetes, chronic systemic disease, infections, vaginal bleeding, cervical shortening, and polyhydramnios—have been consistently identified across large cohorts and systematic reviews as key contributors to preterm birth, underscoring the importance of early detection and guideline-based management to improve maternal and neonatal outcomes [24,p. 494].

#### 1.2.1.3 Maternal obstetric and medical history

Preterm birth (PTB) exhibits a well-documented tendency for recurrence, significantly elevating the risk for women with a prior history of preterm delivery [17,p. 1540]. A recent large U.S. population-based cohort study by Harper et al. reported a 31% recurrence rate among women with a previous spontaneous PTB, with recurrence risk increasing substantially when the earlier PTB occurred before 34 weeks' gestation [83,84].Similarly, Ananth et al. [85], through an extensive population-based analysis of 154,809 pregnancies, found that the likelihood of spontaneous PTB in subsequent pregnancies was markedly higher for women with a prior history, with an odds ratio (OR) of 3.6 (95% CI: 3.2–4.0). These findings are strongly supported by a comprehensive systematic review and meta-analysis, which reported that a previous spontaneous PTB increases recurrence risk to approximately 30% [17,p. 1540], and that recurrence risk rises sharply when the initial PTB occurred at very early gestational ages. A recent population-based cohort study from East Asia further confirmed a precise dose–response pattern: the younger the gestational age at first birth, the higher the risk of recurrence in the subsequent pregnancy [86]. Mechanistically, recurrent PTB is understood to arise from persistent biological vulnerabilities—including genetic predispositions, subtle uterine or cervical structural abnormalities, chronic inflammatory activation, and an exaggerated decidual or immune response to pregnancy. A mechanistic review has highlighted the role of multiple feto-maternal signaling pathways and chronic inflammatory cascades in recurrence patterns [29,p. 56]. Together, these findings confirm that prior PTB is among the strongest predictors in obstetric history.

Preterm birth is also significantly more common in women with multiple pregnancies (twins, triplets, or higher-order multiples) due to increased uterine and placental demands [24,p. 494]. Schaaf et al. [86,p. 76], in a nationwide UK multicenter analysis of 1,451,246 pregnancies, reported that preterm birth occurred far more

frequently among multiple gestations than singletons (47.7% vs. 7.7%; P = 0.047). These observations are supported by meta-analyses and large datasets from the U.S., Nordic countries, and Australia, which consistently show a 4- to 6-fold increased risk of PTB in twins and an even greater risk in triplets, as demonstrated in considerable population-based cohort research from Sweden and the United States [66,p. 1106].

The mechanisms underlying this association are multifactorial and include uterine overdistension, increased myometrial stretch, placental insufficiency, higher rates of preeclampsia, and increased susceptibility to PPROM [23,p. 13]. As more pregnancies involve assisted reproductive technologies (ART), additional studies have shown that ART-related twin pregnancies have similar or higher risks of PTB compared to spontaneously conceived twins, further underscoring the importance of specialized antenatal care in this population [24,p. 494].

A short interpregnancy interval (IPI) is another well-established risk factor for preterm birth. A recent multi-country cohort study including 4.7 million pregnancies demonstrated that an interpregnancy interval shorter than 6 months significantly increases the risk of preterm birth, even after extensive adjustment for maternal characteristics [87]. This association has been consistently observed across multiple systematic reviews and meta-analyses, including WHO-supported pooled analyses, which demonstrate that IPIs shorter than 6 months significantly increase the risk of PTB, low birth weight, and neonatal mortality [24,p. 494]. Proposed mechanisms include insufficient time for uterine involution, which typically takes at least 6 weeks postpartum, and inadequate replenishment of maternal nutrient stores—particularly folate and iron—essential for placental development [26,p. 172]. Biological stress, maternal inflammation, and reduced opportunity for preconception care in closely spaced pregnancies may further contribute [1,p. 15]. Recent cohort studies from the United States and East Asia also indicate that very long IPIs (>5 years) are associated with increased PTB risk, forming a U-shaped relationship [84,p. 9123]. This is thought to reflect the loss of adaptive physiological changes from the previous pregnancy.

Additional elements of obstetric history have also been associated with preterm birth in large-scale studies [85,p. 518]. Women with a history of multiple first-trimester miscarriages or second-trimester pregnancy losses have a significantly higher risk of subsequent PTB, with meta-analyses showing a 1.6- to 2.2-fold increased risk depending on loss timing [88]. Similarly, a history of uterine surgery, such as cone biopsy, large myomectomy, or repeated cesarean sections, has been linked to increased PTB risk, mainly due to cervical insufficiency or impaired uterine contractility [76,p. 158]. Large registry studies from Sweden, Denmark, and Canada show that prior cervical excisional procedures (LEEP/conization) increase the risk of spontaneous PTB by 60–200%, with deeper or larger excisions associated with substantially higher risk [89].

Collectively, maternal obstetric and medical history—including prior preterm birth, multiple gestation, short or long interpregnancy interval, recurrent pregnancy loss, and previous uterine or cervical procedures—constitutes one of the most potent predictors of future preterm delivery. These factors represent enduring reproductive

vulnerabilities that require targeted surveillance, early interventions, and individualized antenatal care strategies.

#### 1.2.1.4 Maternal lifestyle and behavioral factors

Maternal lifestyle and behavioral factors play a substantial role in the risk of preterm birth (PTB) [90]. Among these, substance use during pregnancy is one of the most consistently documented contributors to adverse neonatal outcomes [91]. Lejeune et al. [90,p. 147] conducted a retrospective analysis of 170 pregnant women using two or more substances—such as morphine, cocaine, opioids, cigarettes, ethanol, marijuana, amphetamines, benzodiazepines, or psychiatric medications—and found that the incidence of preterm birth was 22.2% [92]. Notably, the incidence increased from 17.3% among women using three or fewer substances to 31.3% in those using four or more ($P < 0.001$) [92,p. 108].

These results are consistent with broader population-based studies showing that maternal use of both illicit and prescription drugs is associated with markedly higher rates of preterm delivery and neonatal morbidity [93]. Systematic reviews further support these findings [94]. A meta-analysis of over 30 studies reported that cocaine, opioids, and methamphetamines significantly increase the risk of spontaneous and medically indicated PTB, mainly due to placental vasoconstriction, impaired uteroplacental blood flow, and altered neuroendocrine signaling [95].

Similarly, tobacco smoking—one of the most prevalent exposures—has been repeatedly shown to increase PTB risk by 20–60% in a dose-dependent fashion, as demonstrated in large cohorts from the United States, Europe, and Japan [96]. Meanwhile, prenatal exposure to cannabis has been associated with higher rates of low birth weight and PTB in several cohort studies. However, the magnitude of risk varies by frequency and concurrent substance use [97]. The mechanisms by which substance use contributes to PTB are multifaceted [98]. Many drugs of abuse readily cross the placenta and can directly affect fetal development, activate inflammatory pathways, or disrupt the fetal hypothalamic–pituitary–adrenal axis, thereby triggering early labor [99]. In addition, substance use is associated with impaired placental function, increased oxidative stress, and heightened uterine irritability [100]. Alcohol consumption during pregnancy may similarly alter placental perfusion and inflammatory cytokine expression, contributing to early delivery [101].

Behavioral factors also indirectly influence PTB risk through reduced adherence to antenatal care, nutritional deficiencies, and comorbid psychiatric conditions [102]. Given these risks, it is critical for healthcare providers to routinely screen for substance use and offer supportive interventions [103]. Evidence shows that behavioral counseling, addiction treatment referrals, and integrated prenatal care improve outcomes and reduce the risk of PTB in women with substance use disorders [104]. Structured screening using validated tools (e.g., 4Ps Plus, CRAFFT, T-ACE) is recommended in many international guidelines to identify at-risk women early in pregnancy [105].

Overall, maternal lifestyle and behavioral exposures—including tobacco, alcohol, illicit drugs, and polysubstance use—represent modifiable risk factors for preterm birth

[106]. Comprehensive and nonjudgmental prenatal care that incorporates early screening, counseling, and tailored cessation support is essential for mitigating these risks and improving maternal and neonatal outcomes [107].

#### 1.2.1.5 Maternal physical and mental stress and preterm birth

Extensive physical labor and high levels of mental stress during pregnancy are well-established risk factors for adverse pregnancy outcomes, including preterm birth [108]. A multicenter case-control study by Saurel-Cubizolle et al., involving 13,056 cases, found that pregnant women exposed to heavy physical demands—such as prolonged standing, lifting heavy objects, repetitive bending, or work requiring sustained exertion—had a significantly increased risk of preterm birth (OR = 1.33, 95% CI 1.1–1.6) [109].

These findings are consistent with multiple occupational health studies demonstrating that physically strenuous work is associated with higher rates of spontaneous preterm labor, premature rupture of membranes, and placental disorders [110]. Meta-analyses have further shown that maternal workloads exceeding 40 hours per week, prolonged standing (>6 hours/day), and shift work—particularly night shifts—are associated with modest but significant increases in the risk of preterm birth [111]. Physiologically, excessive physical strain may exacerbate uterine irritability, reduce uteroplacental blood flow, and trigger mechanical or hormonal pathways that precipitate early delivery [112]. In addition to physical strain, psychological stress, emotional distress, and inadequate social support have strong associations with preterm birth [113]. A retrospective case analysis by Copper et al. reported that pregnant women experiencing increased mental and emotional stress had nearly twice the likelihood of delivering prematurely (OR = 1.16, P = 0.003) [114].

Further evidence from extensive cohort studies—including the Pregnancy Risk Assessment Monitoring System (PRAMS), the Avon Longitudinal Study of Parents and Children (ALSPAC), and Scandinavian national registries—demonstrates that chronic psychosocial stress, anxiety, depression, and exposure to significant life events significantly elevate the risk of preterm birth [115]. Systematic reviews and meta-analyses have confirmed that maternal stress is a consistent predictor, with risk increasing proportionally to the severity, chronicity, and timing of stress exposure [116].

Biologically, stress is believed to influence preterm birth by activating the maternal hypothalamic–pituitary–adrenal (HPA) axis [117]. Chronic stress leads to sustained elevations in cortisol and corticotropin-releasing hormone (CRH), which can prematurely stimulate prostaglandin production, cervical ripening, and uterine contractility [118]. Stress-induced inflammation, oxidative stress, and endothelial dysfunction may further contribute to placental aging and early parturition [119]. Additionally, psychological stress has been associated with higher rates of behavioral risk factors—such as poor sleep, reduced prenatal care utilization, and inadequate nutrition—that may compound vulnerability to preterm labor [120].

Importantly, stress does not act in isolation; it often interacts with other biological and social factors, including maternal comorbidities, occupational exposures, intimate

partner violence, and environmental challenges [121]. Low social support, interpersonal conflict, and financial strain have been shown to magnify the effects of maternal stress on preterm birth risk [122]. Conversely, studies demonstrate that interventions such as stress-reduction programs, mindfulness-based therapy, workplace modifications, and enhanced prenatal support can help mitigate these risks [123]. Overall, both physical and psychological stress represent modifiable risk factors for preterm birth [124]. Their prevention requires a combined approach of occupational adjustments, mental health support, and comprehensive prenatal care, particularly for women exposed to high workloads or chronic psychosocial stress [125].

### 1.2.2 Fetal factors

Fetal factors play a crucial role in the etiology of preterm birth, reflecting conditions intrinsic to the fetus that can disrupt normal gestational progression [29,p. 56]. Unlike maternal or environmental determinants, fetal risk factors often arise from developmental abnormalities, genetic conditions, or complications in fetal presentation that directly influence uteroplacental function and fetal well-being [30,p. 77]. These conditions may trigger spontaneous preterm labor, contribute to premature rupture of membranes, or necessitate medically indicated early delivery due to concerns for fetal compromise [40,p. 556].Understanding fetal contributors—such as congenital malformations, pregnancies conceived through assisted reproductive technologies, and abnormal fetal presentation—is essential for early identification of at-risk pregnancies and for guiding timely interventions aimed at reducing preterm birth and improving perinatal outcomes [23,p. 13].

#### 1.2.2.1 Congenital malformations

Congenital malformations have been identified as an independent risk factor for premature birth, with important implications for both maternal and neonatal outcomes [106,p. 494]. Research suggests that around 15% of fetuses or newborns with major congenital anomalies are delivered preterm, indicating a strong association between structural abnormalities and early delivery. Large population-based data from France (EPICARD study) showed that approximately 15% of infants with congenital heart defects (CHD) were born before 37 weeks ’gestation and that the odds of preterm birth in infants with CHD were more than two times higher than in the general population, with particularly elevated risk for very preterm birth before 32 weeks [24,p. 494]. A French epidemiological study that analyzed 2,189 fetuses with CHD, excluding atrial septal defects, similarly reported that 13.5% were delivered preterm, with the likelihood of preterm birth in fetuses with CHD being about twice as high as in healthy fetuses [126]. Recent cohort data from the Mutaba’ah study in the United Arab Emirates further support this association, showing that neonates with any significant congenital anomaly had approximately double the odds of preterm birth compared with those without anomalies (adjusted OR = 2.0), and that the presence of multiple anomalies increased the odds of preterm delivery more than fivefold [127].

The relationship between congenital malformations and prematurity appears to be bidirectional: infants with anomalies are more likely to be born preterm, and preterm infants are more likely to have congenital anomalies compared with term infants [128]. A recent narrative review emphasized that these conditions frequently co-exist and that the combined burden of prematurity and congenital anomalies leads to a greater-than-additive risk of mortality, brain injury, and long-term neurodevelopmental impairment [129]. Specific anomaly groups—such as complex CHD, neural tube defects, diaphragmatic hernia, abdominal wall defects, and chromosomal abnormalities—are particularly associated with early and medically indicated preterm birth, often because of persistent fetal compromise, polyhydramnios, growth restriction, or the need to deliver early to enable specialized neonatal or surgical care [130]. Physiologically, congenital malformations may contribute to preterm birth through altered fetal hemodynamics, chronic hypoxia, impaired placental function, or mechanical factors (e.g., severe polyhydramnios or reduced uterine space) [131]. From a clinical standpoint, the recognition that major congenital anomalies substantially increase the risk of preterm birth underscores the importance of early prenatal diagnosis, detailed fetal echocardiography and anomaly scanning, and multidisciplinary management in tertiary centers, with careful timing of delivery to balance the risks of extreme prematurity against those of ongoing in utero compromise for both the mother and the fetus [132].

1.2.2.2 Assisted reproductive technology and preterm birth

The increasing use of assisted reproductive technologies (ART), particularly in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has been consistently associated with a heightened risk of preterm birth [24,p. 494]. Numerous studies, both domestic and international, have reported this connection, with one meta-analysis estimating an odds ratio (OR) of 0.8 (95% CI: 0.69–0.93) for preterm birth in pregnancies conceived through IVF compared with natural conception [106,p. 494]. Most large cohort studies and systematic reviews, however, indicate that ART-conceived singleton pregnancies have higher rates of preterm delivery than spontaneously conceived pregnancies, with pooled ORs generally in the range of 1.4–1.8 after adjustment for maternal age, parity, and other confounders. This suggests that ART, underlying infertility, or both contribute to an increased susceptibility to early delivery [74,p. 581].

One study that conducted a case analysis of 566 pregnancies in women aged 35 years and above compared outcomes between natural conceptions and those achieved through IVF. The results showed a significantly higher incidence of preterm birth in the IVF group (18.7% vs. 10.3%; $P < 0.008$) [133]. Large population-based studies from Nordic countries, the United Kingdom, and the United States have reported similar patterns, with ART singleton pregnancies showing increased risks of both spontaneous and medically indicated preterm birth, as well as higher rates of very preterm birth (<32 weeks) [134]. Importantly, while multiple gestation (twins, triplets) contributes substantially to this excess risk, elevated preterm birth rates persist even

among singleton ART pregnancies, indicating that ART-related or infertility-related factors are involved beyond multiplicity alone [135].

Several mechanisms have been proposed to explain the association between ART and prematurity. First, women undergoing ART are often older and may have a longer history of subfertility, both of which are independently associated with adverse pregnancy outcomes [136]. Second, ovarian stimulation and embryo culture conditions may alter endometrial receptivity or early placentation, potentially contributing to abnormal trophoblast invasion, placental insufficiency, and increased risk of hypertensive disorders or fetal growth restriction, which in turn necessitate medically indicated preterm delivery [137,138]. Third, higher rates of placenta previa, placenta accreta spectrum, and abnormal cord insertion have been observed in ART pregnancies, further increasing the likelihood of early delivery [139]. Emerging evidence also suggests potential epigenetic and imprinting alterations associated with ART and cryopreservation techniques, which may influence placental development and fetal growth [140,141].

To mitigate these risks, many countries have moved toward single-embryo transfer (SET) policies and more conservative ovarian stimulation protocols. Evidence from national ART registries across Europe, Australia, and North America shows that SET policies have significantly reduced the incidence of high-order multiple pregnancies and lowered the overall burden of preterm birth associated with ART [142, 143]. However, these strategies have not eliminated the elevated risk of preterm birth among ART-conceived singletons, as population-based studies continue to demonstrate higher rates of both spontaneous and medically indicated preterm delivery even after adjustment for confounders [144]. Therefore, pregnancies achieved through ART—particularly in older women or those with long-standing infertility—are now widely regarded as high-risk and warrant careful antenatal surveillance, early detection and management of maternal complications, and individualized planning of delivery. These findings emphasize the importance of counseling couples about the potential obstetric risks associated with ART and of providing tailored, multidisciplinary care to minimize complications, including preterm delivery [145,146].

#### 1.2.2.3 Abnormal fetal presentations

Abnormal fetal presentations, particularly breech, transverse, or oblique lie, have been consistently associated with an increased likelihood of preterm birth. A large population-based analysis from Hong Kong demonstrated that non-cephalic fetal positions were strongly associated with higher rates of preterm delivery even after adjustment for maternal and obstetric factors [147]. Recent nationwide registry studies from Europe, Australia, and North America have similarly confirmed that 20–30% of breech presentations occur before 37 weeks, highlighting a robust association between malpresentation and both spontaneous and medically indicated preterm birth [148, 149]. Importantly, this association is bidirectional: abnormal presentations may predispose to preterm labor, while earlier gestational age increases the likelihood of unstable or non-cephalic fetal lie due to greater fetal mobility [150].

The mechanisms underlying this association remain incompletely understood. Several anatomical and physiological pathways have been proposed. Uterine abnormalities—such as bicornuate uterus, septate uterus, or significant leiomyomas—may restrict fetal rotation and simultaneously increase uterine irritability [151]. Placental factors, including placenta previa and posterior or fundal low-lying placenta, have been linked to persistent breech presentation and increased risk of antepartum hemorrhage, both of which may necessitate early delivery [152]. Amniotic fluid disturbances also contribute: polyhydramnios may lead to unstable lie, while oligohydramnios limits fetal repositioning and frequently signals placental insufficiency—an established risk factor for preterm birth [153].

Abnormal presentations are also more common in pregnancies complicated by fetal growth restriction, congenital anomalies, neuromuscular impairment, or maternal pelvic abnormalities, all of which independently elevate the risk of preterm labor. Large multicenter cohort studies have shown that breech presentation is more prevalent in fetuses with chromosomal anomalies, structural malformations, or impaired fetal tone, indicating that intrinsic fetal factors may drive both malpresentation and preterm birth simultaneously [154-155]. Additionally, malpresentation at term is strongly associated with prior obstetric history, including earlier preterm birth or previous cesarean delivery, further complicating causal pathways [156].

Clinically, this relationship underscores the need for routine assessment of fetal position during antenatal care. External cephalic version (ECV) has been demonstrated in large trials and updated meta-analyses to reduce the incidence of term breech presentation and may, in some cases, lower the likelihood of preterm birth by stabilizing fetal lie [157]. However, ECV success rates are lower in early gestation and in the presence of uterine anomalies, fetal growth restriction, oligohydramnios, or placenta previa [158]. As such, pregnancies with abnormal fetal presentation require individualized monitoring, early identification of coexisting risk factors, and multidisciplinary planning to optimize maternal and neonatal outcomes.

### 1.2.3 Environmental factors

Environmental factors are increasingly recognized as a domain influencing the risk of preterm birth, acting through complex interactions among maternal physiology, placental function, and fetal development [159]. Unlike demographic or medical determinants, environmental exposures often operate at the population level and may affect large groups of pregnant women simultaneously [160]. Key environmental contributors identified in epidemiological studies include ambient air pollution, extreme temperatures, environmental toxins, heavy metals, household air pollution, and occupational exposures [161-162]. These exposures can trigger systemic inflammation, oxidative stress, endocrine disruption, or placental dysfunction—pathways central to the initiation of preterm labor [163-164]. Evidence from North America, Europe, and Asia shows that adverse environmental conditions significantly elevate the risk of early delivery, often independent of socioeconomic status or maternal comorbidities [165-167]. Understanding and mitigating these ecological risks is therefore essential for comprehensive preterm birth prevention, especially in rapidly

urbanizing or industrialized regions where pollutant levels and climate-related stressors continue to rise [168-169].

1.2.3.1 Air pollution and preterm birth

A growing body of epidemiological research has established that maternal exposure to ambient air pollution is a significant and independent risk factor for preterm birth. Population-based cohorts from North America, Europe, and Asia consistently demonstrate that pollutants such as fine particulate matter (PM2.5 and PM10), nitrogen dioxide (NO2), and ozone (O3) increase the risk of both spontaneous and medically indicated preterm delivery. A global cohort analysis involving more than 53 million births across nine countries reported that each 10 μg/m³ increase in PM2.5 during pregnancy was associated with an 11% rise in preterm birth risk (RR = 1.11; 95% CI: 1.05–1.17), with the strongest associations observed during the third trimester [170,171]. An updated systematic review of 68 studies further confirmed that PM2.5 exposure during late pregnancy increased the risk of preterm birth by approximately 13%, whereas NO2 increased the risk by 9% per 10 μg/m³ increment [172].

Evidence from national birth registries enhances these findings. In the California Birth Cohort, which includes over three million births, long-term exposure to elevated PM2.5 and NO2 was associated with a 15–19% higher risk of spontaneous preterm birth after adjustment for maternal and neighborhood confounders [173]. Similarly, population-level research in Ontario, Canada, showed that chronic exposure to PM2.5 above 8 μg/m³ increased the risk of preterm birth by 12% [174]. Time-series analyses in Seoul demonstrated that short-term NO2 peaks during the final six weeks of gestation increased the risk of preterm birth by 8–14%, highlighting the sensitivity of late pregnancy to pollution fluctuations [174,p. 836]. Studies from Taiwan and China further support the role of acute exposure: transient PM2.5 spikes during the last 4–8 weeks of pregnancy significantly increased the incidence of early labor, suggesting that air pollutants may act as triggers during critical windows of gestation [175]. Significantly, PTB rates rise most sharply when PM2.5 levels exceed 25–30 μg/m³, a threshold commonly reached in highly polluted regions [175,p. 112].

Emerging mechanistic evidence provides biological plausibility for these epidemiological associations. Pollutants such as PM2.5 and O3 induce systemic inflammation, oxidative stress, endothelial dysfunction, and impaired placental angiogenesis. Studies consistently report increased maternal inflammatory cytokines (e.g., IL-6, TNF-α), elevated oxidative stress markers, and disrupted vascular remodeling in placentas exposed to higher concentrations of particulate matter [176]. Placental studies show reduced villous density, impaired trophoblast invasion, and increased calcification among women living in areas with high pollution levels. Epigenetic alterations, including DNA methylation changes in genes involved in immune regulation and placental development, have also been documented in association with pollution exposure [177], suggesting long-lasting effects on fetal growth and pregnancy maintenance.

Clinically, air pollution exposure has been linked not only to preterm birth but also to related obstetric complications that increase the likelihood of early delivery,

including preterm premature rupture of membranes (PROM), placental abruption, hypertensive disorders of pregnancy, and fetal growth restriction [178]. Extreme pollution events offer additional evidence through natural experiments: wildfire smoke episodes in California, during which PM2.5 frequently exceeded 100–300 μg/m³, were associated with 6–15% increases in preterm birth rates within affected counties [179]. Similar patterns have been observed during severe urban smog episodes in China and South Asia, where abrupt increases in particulate levels corresponded to measurable spikes in preterm delivery.

Given the robust evidence linking air quality to preterm birth, multiple clinical and public health organizations have emphasized the need for targeted preventive strategies during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) has recommended that clinicians advise pregnant women to minimize outdoor activity on high-pollution days, use indoor air purifiers, improve ventilation, and follow Air Quality Index alerts to reduce exposure during vulnerable gestational periods [180,181]. Public health interventions, including national clean-air policies, reductions in traffic emissions, and urban environmental planning, have been associated with measurable declines in preterm birth rates; for example, implementation of China's Clean Air Action Plan led to significant improvements in maternal air quality exposure and corresponding reductions in early delivery [182,183]. These findings highlight air pollution as a modifiable environmental determinant of preterm birth and underscore the importance of integrating ecological health considerations into national maternal and child health strategies [184].

1.2.3.2 Extreme temperature exposure and preterm birth

Extreme ambient temperatures, both heat and cold, have emerged as significant environmental determinants of preterm birth (PTB), supported by robust epidemiological evidence across multiple continents. Large multicenter cohort studies from the United States, China, Australia, and Southern Europe consistently demonstrate that exposure to extreme heat, particularly in the last weeks of pregnancy, increases the risk of spontaneous preterm labor. A landmark California cohort study by Basu et al., examining more than 58,000 preterm births, found that maternal exposure to high ambient temperatures and heatwaves during the seven days preceding delivery increased PTB risk by 8–21%, with the most potent effects observed for heatwaves lasting three or more days [185]. Similar results were observed in a nationwide U.S. cohort of 2.2 million births, in which late-gestation heat exposure was associated with a significantly increased risk of PTB, particularly before 34 weeks' gestation [186].

Meta-analyses further confirm these findings. An updated systematic review and meta-analysis of 47 studies concluded that each 1–2°C increase above local temperature thresholds was associated with a 1.05–1.16-fold increase in the relative risk of preterm birth [187]. Time-series analyses performed in Guangzhou and Sydney have likewise demonstrated that incremental increases above regional heat thresholds significantly increase the risk of PTB, with critical windows occurring during the week immediately preceding delivery [188-189]. Case-crossover studies from California and

Brisbane also report 10–20% higher odds of preterm birth during heatwave periods compared with non-heatwave periods [190-191].

The biological mechanisms underlying heat-related PTB include maternal dehydration, reduced uteroplacental perfusion, peripheral vasodilation, cardiovascular strain, and increased production of inflammatory cytokines. Heat exposure has also been shown to activate the maternal–fetal stress axis and increase circulating cortisol and corticotropin-releasing hormone (CRH), promoting early initiation of labor pathways [192].

Conversely, exposure to extremely low temperatures also increases the risk of PTB. Large population-based studies from Canada, Northern China, and Scandinavia show that maternal exposure to cold extremes—particularly during the second and third trimesters—increases the risk of preterm birth by 8–15% [193-195]. Proposed mechanisms include cold-induced vasoconstriction, reduced placental perfusion, systemic inflammation, and maternal blood pressure fluctuations, all of which can disrupt placental function and precipitate early labor.

Seasonal analyses consistently reveal clustering of preterm births in the hottest summer months and coldest winter periods, even after adjusting for pregnancy infections, influenza epidemics, air pollution, and socioeconomic status [196]. With global climate change expected to increase the frequency, duration, and intensity of extreme temperature events, the temperature–PTB relationship is projected to become increasingly important for public health. Modeling studies project that heat-related preterm births may increase substantially in the coming decades if temperatures continue to rise [197-198]. Collectively, this evidence underscores the critical need for climate-informed prenatal care. Public health strategies—including heatwave and cold-spell alerts, improved housing insulation and ventilation, and education on minimizing exposure—represent essential components of preterm birth prevention in the context of a changing climate.

#### 1.2.3.3 Exposure to heavy metals and preterm birth

Exposure to heavy metals, including lead, mercury, cadmium, and arsenic, has emerged as an important environmental determinant of preterm birth (PTB), supported by a growing body of epidemiological, toxicological, and mechanistic evidence. Even low-level exposure during pregnancy can impair placental function and disrupt fetal development, increasing susceptibility to early delivery.

Lead is among the most extensively studied heavy metals in relation to PTB. Meta-analyses of prospective cohort studies from the United States, Mexico, and China consistently show that elevated maternal blood lead levels are associated with a 1.3–1.8-fold increase in the risk of preterm birth after adjustment for key confounders [199-200]. Lead readily crosses the placenta, accumulates in fetal tissues, and interferes with trophoblast differentiation, placental angiogenesis, and oxidative balance. These processes contribute to chronic inflammation, increased maternal blood pressure, and shortened gestational length. Notably, adverse effects have been observed even at blood lead concentrations below the previously accepted safety thresholds.

Mercury, particularly methylmercury, primarily obtained through fish consumption, has also been associated with preterm birth. Cohort studies from Japan, Norway, and Mediterranean countries demonstrate that higher maternal blood or hair mercury concentrations are associated with increased PTB risk, with stronger effects observed among women with low intake of protective nutrients such as selenium and omega-3 fatty acids [201,202]. Mechanistic studies suggest that mercury induces mitochondrial damage, oxidative stress, and impaired placental vascularization, thereby compromising fetal oxygenation and promoting early labor.

Arsenic, a significant contaminant in drinking water in parts of South Asia, Central Asia, and South America, is strongly linked to adverse birth outcomes. Large population-based studies from Bangladesh, India, and Chile report that chronic exposure to inorganic arsenic in groundwater increases the risk of PTB by 20–60%, with dose–response relationships indicating higher risk at concentrations exceeding WHO guidelines [203-205]. Arsenic disrupts endocrine signaling, impairs placental differentiation, and causes widespread epigenetic alterations, including DNA methylation changes, that may predispose the fetus to early delivery.

Emerging evidence implicates cadmium as another relevant toxicant. Studies from the U.S. National Children's Study and Chinese birth cohorts have found that higher maternal urinary cadmium levels are associated with increased risk of PTB, likely mediated by placental oxidative stress, impaired nutrient transport, and altered inflammatory signaling [206].

Collectively, these findings demonstrate that exposure to heavy metals represents a critical and preventable environmental threat to maternal–fetal health. Public health interventions, including improving water quality, reducing industrial emissions, phasing out lead-based products, and providing guidance on safe fish consumption, are essential strategies for mitigating exposure. Clinically, evaluating potential sources of environmental, dietary, or occupational exposure during antenatal care can help identify at-risk pregnancies and guide individualized counseling to reduce the risk of preterm birth.

#### 1.2.3.4 Occupational chemical exposure

Occupational exposure to chemical agents during pregnancy has been shown to increase the risk of preterm birth through several well-characterized pathways. Evidence from large epidemiological datasets demonstrates that exposure to organic solvents is particularly harmful. A French prospective cohort of 3,300 pregnant workers showed that women exposed to glycol ethers had a 1.44-fold higher risk of preterm birth (adjusted RR 1.44; 95% CI 1.02–2.05) compared with unexposed women [207]. Similarly, a U.S. National Birth Defects Prevention Study reported that maternal occupational exposure to aromatic hydrocarbons was associated with a 0.6–0.9-week reduction in gestational age and a 40% increase in the risk of PTB (adjusted OR 1.40; 95% CI 1.10-1.78) [208]. Additional evidence from a Finnish industrial workforce cohort demonstrated that exposure to mixed solvents increased the risk of medically indicated preterm birth by 65% (adjusted OR 1.65; 95% CI 1.18-2.29) [209].

Pesticide exposure has also been repeatedly linked to preterm birth. The U.S. Agricultural Health Study, analyzing more than 34,000 pregnancies, found that women with direct exposure to organophosphate pesticides experienced a preterm birth rate of 11.1%, compared with 7.3% among non-exposed agricultural workers (adjusted OR 1.48; 95% CI 1.21–1.81) [210]. A Brazilian cohort of 1,221 pregnancies exposed to pyrethroids reported a twofold increased risk of PTB (adjusted OR 2.05; 95% CI 1.31–3.18) [211]. Meanwhile, a multicenter prospective study from Thailand demonstrated that urinary metabolites of chlorpyrifos were significantly associated with a 0.5-week reduction in gestational age and a 29% increase in PTB risk (RR 1.29; 95% CI 1.08–1.53) [212].

Increasingly, research shows that endocrine-disrupting chemicals (EDCs) exert substantial effects on pregnancy duration. In the U.S. HOME Study, higher maternal concentrations of DEHP metabolites were associated with a 1.52-fold higher risk of spontaneous PTB (adjusted OR 1.52; 95% CI 1.10–2.08) [213]. A large NICHD cohort confirmed that women in the highest quartile of phthalate exposure had double the likelihood of PTB (adjusted OR 1.91; 95% CI 1.23–2.96) [214]. Prospective studies from Korea found that bisphenol A (BPA) levels above the 75th percentile were associated with a 0.9-week reduction in gestational duration and a 47% increased risk of PTB (adjusted OR 1.47; 95% CI 1.12–1.92) [215]. A recent meta-analysis of 12 cohorts further demonstrated that maternal BPA exposure increased the odds of preterm birth by 28% (pooled OR 1.28; 95% CI 1.09–1.51) [216].

Mechanistic studies provide biological plausibility for these associations. Placental tissue analyses from exposed women show that solvents impair trophoblast invasion, disrupt vascular endothelial growth factor (VEGF) pathways, and generate oxidative DNA damage—mechanisms that can induce early labor [217]. Pesticides have been observed to reduce placental mitochondrial function and to increase pro-inflammatory cytokines such as IL-6 and TNF-α, both of which are strongly linked to the preterm labor cascade [218]. EDCs disrupt progesterone receptor expression and thyroid hormone signaling and induce abnormal DNA methylation at key placental regulatory regions [219]. These pathways align with the clinical patterns of shortened gestation observed in exposed populations.

Given the strength of this evidence, professional organizations—including the American College of Obstetricians and Gynecologists and the International Federation of Gynecology and Obstetrics—recommend routine screening for occupational chemical exposures during prenatal visits [220]. Public-health interventions such as improved workplace ventilation, substitution of hazardous chemicals, enhanced use of personal protective equipment, and reassignment of pregnant workers away from solvent or pesticide exposure have been shown to reduce biomarkers of maternal chemical exposure by 30–60% in intervention studies [221].

### 1.2.4 Genetic factors

Genetic susceptibility plays an increasingly recognized role in the pathophysiology of preterm birth (PTB), with evidence that both maternal and fetal genomes contribute to the timing of parturition. Family and twin studies have shown

that PTB clusters within families and that women who were themselves born preterm, or who have a family history of PTB, are at significantly increased risk of delivering preterm, suggesting a heritable component [222,223]. Recent genome-wide association studies (GWAS), exome sequencing, and systematic reviews confirm that variants in genes involved in inflammation, immune regulation, endocrine pathways, extracellular matrix remodeling, vascular function, and uterine contractility contribute to variation in gestational duration and susceptibility to spontaneous PTB [224-226]. Notably, modern parent–offspring GWAS demonstrate that maternal and fetal genetic effects are partially distinct and sometimes even antagonistic, highlighting the complex interplay between the two genomes in controlling the onset of labor [227,228].

1.2.4.1 Maternal genetic variants and preterm birth

Maternal genetic variants contribute to the regulation of the intrauterine environment by influencing immune responses, hormonal signaling, metabolic pathways, vascular and myometrial function. Candidate-gene and hypothesis-free genomic studies have identified several maternal loci associated with gestational duration and PTB [228,p. 119].

Study by McElroy et al. identified rare coding variants in the maternal complement receptor 1 (CR1) gene that were strongly associated with spontaneous idiopathic PTB (OR=1.7), implicating dysregulated complement activation and exaggerated inflammatory responses in the pathogenesis of early labor [222,p. 303]. Research team by Bream et al. used a linkage candidate-gene approach in PTB-segregating families. They found evidence that several maternal variants—ENPP1, IGFBP3, DHCR7, and TRAF2—were associated with PTB, pointing to roles for insulin signaling, growth factor regulation, cholesterol metabolism, and TNF-related inflammatory signaling in maternal susceptibility [229]. Rocha et al. subsequently demonstrated that two RLN2 promoter polymorphisms (rs4742076 and rs3758239) in Filipino women were associated with spontaneous PTB and preterm premature rupture of membranes (PPROM), supporting a mechanistic role for relaxin in cervical remodeling and membrane integrity [230].

Over the past decade, large-scale GWAS have refined our understanding of the maternal genetic architecture. Work from the INTERGEN and allied consortia led by Zhang and colleagues has identified maternal loci near *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C* associated with gestational duration, with variants at *EBF1*, *EEFSEC*, and *AGTR2* also linked specifically to PTB [227,p. 8569]. These genes have biologically plausible roles in uterine development, vascular regulation, and endocrine signaling. More recently, a large parent–offspring meta-analysis by Solé-Navais et al. confirmed that many of these loci act primarily through maternal effects on gestational duration, with substantial overlap between maternal genetic influences on gestational length and risk of preterm delivery, as well as shared effects on fetal birth weight [231].

Inflammatory and cytokine genes remain a significant focus. A recent systematic review and meta-analysis by Mladenić et al. evaluated 81 studies of maternal genetic risk factors for spontaneous PTB. They found that, despite considerable heterogeneity,

the TNF-α rs1800629 (−308G>A) polymorphism a modestly but consistently associated with spontaneous PTB across multiple populations [232]. That review, together with earlier candidate-gene studies summarized by Strauss et al., also highlights functional variants in IL6, IL10, IL1B, NOS3, SERPINE1 and other immune/coagulation genes that may shift the balance between pro- and anti-inflammatory signaling at the maternal–fetal interface and contribute to premature activation of inflammatory pathways and early labor [232,p. 18].

Newer exome-based approaches have identified additional maternal susceptibility genes. Huusko et al. used whole-exome sequencing in Finnish and US families with recurrent spontaneous PTB. They discovered rare, likely damaging variants in *HSPA1L*, a heat-shock protein involved in glucocorticoid receptor signaling, suggesting that altered maternal stress-response and chaperone function may predispose to earlier onset of labor [233] Subsequent exome-wide work (e.g., Biggio et al.) has supported a role for rare coding variants in multiple maternal genes in susceptibility to spontaneous PTB [232,p. 18].

Together, these studies support a model in which maternal genetic variation in complement pathways (CR1), cytokines and immune signaling (TNF, IL6, IL10, TRAF2 and related networks), endocrine and relaxin signaling (RLN2, ADCY5, WNT4), vascular and renin–angiotensin pathways (AGTR2), and stress-response genes (HSPA1L) collectively modulate gestational duration and vulnerability to spontaneous PTB [222,p. 303] The maternal genome appears to exert a primary influence on when labor starts, and this influence is partly shared with maternal genetic effects on birth weight [231,p. 559].

#### 1.2.4.2 Fetal genetic factors

Fetal genetic variants also contribute meaningfully to PTB risk, often through pathways related to fetal stress responses, placental development, and innate immunity. The fetal genome can influence activation of the fetal hypothalamic–pituitary–adrenal (HPA) axis, inflammatory signaling, and structural development of the placenta and membranes—all key triggers of early labor [231,p. 559].

In the candidate-gene linkage study by Bream et al., fetal variants in CRHR1 and CYP2E1 showed strong evidence of linkage with PTB ($P = 0.001$), suggesting an etiologic role for fetal corticotropin-releasing hormone (CRH) signaling and oxidative stress/xenobiotic metabolism in the etiology of early delivery [229,p. 135]. Fetal CRHR1 variants may enhance activation of the fetal HPA axis, leading to increased CRH production, accelerated maturation, and earlier initiation of the parturition cascade, whereas CYP2E1 variants may augment susceptibility to oxidative stress and toxic metabolites, thereby promoting inflammatory injury in fetal tissues and membranes [229,p. 135].

Beyond these loci, fetal genetic control of innate immunity has been highlighted as a potential contributor to PTB risk. Earlier candidate-gene and small GWAS studies, summarised in recent reviews, identified associations between fetal TLR-pathway polymorphisms and severe prematurity with PROM in some populations. However, results have been inconsistent [224,p. 294]. Other candidate-gene and exome-based

studies have implicated fetal variants in cytokine genes such as IL6, as well as genes involved in extracellular-matrix remodelling and placental angiogenesis (e.g. COL and FLT1 loci). Still, replication has been variable [232,p. 18].

Recent large genome-wide analyses that explicitly partition maternal and fetal effects provide additional insights. Parent–offspring GWAS and meta-analyses show that while maternal genetic influences account for most of the heritability of gestational duration, fetal variants contribute to PTB risk and are particularly important for traits such as birth weight and fetal growth, which, in turn, are linked to gestational length [231,p. 559]. These studies also reveal a complex pattern of antagonistic pleiotropy, in which maternal alleles that prolong gestation are associated with lower fetal birth weight. In contrast, fetal alleles that promote growth are associated with modestly shorter gestations [231,p. 559]. This co-adaptation between maternal and fetal genomes likely evolved to balance the competing demands of fetal development and safe timing of birth.

Overall, current evidence supports a polygenic and multifactorial model in which fetal genetic variation in CRH signaling (CRHR1), oxidative stress and xenobiotic metabolism (CYP2E1), innate immunity (TLR-related pathways, IL6), and extracellular-matrix and vascular development (COL/FLT1 and related genes) interacts with maternal genetic and environmental factors to determine the final timing of parturition [233,p. 100]. While individual fetal variants often confer only modest risk, their combined effect, together with maternal genetic background and environmental exposures, helps explain familial clustering of PTB and the substantial unexplained variability in gestational duration [233,p. 100].

## 1.3 Oral Health and Preterm Birth

The concept that oral infections can provoke systemic disease dates back to Miller's "focal infection theory," which, as early as 1891, identified the mouth as a potential source of distant inflammatory damage [31, p. 73]. Since then, oral health has come to be regarded as an integral component of general health, with dental caries and periodontal disease as the two most prevalent chronic oral conditions worldwide [37,p. 182]. Over the past two decades, research has increasingly focused on whether specific oral health conditions—such as gingivitis, periodontitis, advanced carious lesions, apical periodontitis, and poor overall oral hygiene—are associated with adverse pregnancy outcomes, particularly PTB [38,p. 685].

### 1.3.1 Periodontal status and preterm birth

Periodontal disease, ranging from reversible infection of gingiva to destructive bone tissue loss, is the most intensively studied oral condition in relation to PTB [27,p. 769]. Periodontitis is characterized by a dysbiotic subgingival biofilm, chronic inflammation of the supporting tissues, and progressive loss of periodontal attachment and bone [32,p. 30]. When an infection is present, the body releases white blood cells to combat it, triggering an inflammatory response that results in gum inflammation, redness, and easy bleeding [37, p. 182]. As the gums become inflamed, they may detach from the tooth, creating pockets that allow bacteria to penetrate deeper into the

bone tissue and periodontal ligament, leading to loosening of the tooth and, ultimately, tooth loss. This chronic inflammatory focus can act as a reservoir of bacteria and inflammatory mediators that disseminate systemically, potentially influencing the feto-placental unit. Understanding and addressing periodontal disease are critical not only for maintaining oral health but also for reducing its systemic health implications [37,p. 182].

Recent evidence suggests that periodontal diseases may be one of the significant factors contributing to adverse pregnancy outcomes, particularly preterm birth (PTB), through systemic inflammatory and microbiological pathways. Modern observational studies and meta-analyses consistently report that women with moderate to severe periodontitis have a higher risk of PTB compared with periodontally healthy pregnant women [233,p. 100]. A 2022 global meta-analysis of 45 studies ($n > 75,000$) found that periodontal disease was associated with a 1.6-fold higher risk of PTB (pooled OR 1.61, 95% CI 1.35–1.93) after adjustment for maternal age, smoking, socioeconomic status, and comorbidities [234]. Similarly, an umbrella review published in 2023 concluded that the association, although modest, is consistent and biologically plausible, with the highest risks seen in women with severe periodontitis [24,p. 494].

Recent mechanistic studies further strengthen this link, demonstrating that periodontal pathogens—including Fusobacterium nucleatum, Porphyromonas gingivalis, and Campylobacter rectus—can translocate hematogenously to the placenta, trigger local inflammatory responses, and upregulate cytokines such as IL-1β, IL-6, TNF-α, and $PGE_2$, which are known mediators of cervical ripening and uterine contractility [235,236]. Several contemporary placenta-based metagenomic studies have confirmed that oral bacteria are detected more frequently at the maternal–fetal interface in preterm than in term pregnancies [237].

The question of whether periodontal treatment during pregnancy reduces PTB risk has been extensively re-evaluated in recent years. While early randomized trials yielded inconsistent results, more recent evidence provides a more nuanced understanding. A 2017 individual patient–data meta-analysis (IPD-MA) including >3,500 pregnant women reported that scaling and root planing (SRP) did not significantly reduce PTB rates overall but showed a possible benefit in women with severe baseline periodontitis or coexisting obstetric risk factors [238]. More recent analyses offer more substantial support: a 2024 systematic review and network meta-analysis of nine RCTs ($n \approx 4,000$) found that SRP combined with chlorhexidine mouthwash significantly reduced the risk of PTB (RR 0.44, 95% CI 0.30–0.65) and low birth weight, whereas SRP alone showed weaker effects [239]. Another 2023 meta-analysis demonstrated that early periodontal therapy (before 24–28 weeks) was associated with significant reductions in inflammatory biomarkers, improved periodontal health, and modest reductions in PTB among high-risk subgroups [240].

Despite some persistent disagreement between clinical trials, the contemporary consensus from the 2023 FIGO Working Group on Oral Health and Pregnancy and recent expert reviews is that: Periodontal disease is a modifiable maternal risk factor associated with higher PTB risk; Periodontal treatment during pregnancy is safe and

improves periodontal health; Combining SRP with antimicrobial adjuncts may decrease PTB risk in selected high-risk populations; Preconception or early-pregnancy periodontal care is likely more effective than late gestational treatment [241].

Given these findings, maintaining optimal periodontal health—ideally before conception or early in pregnancy—remains an essential component of maternal care and may help reduce systemic inflammation and improve pregnancy outcomes, even when effects on PTB are moderate.

### 1.3.2 Dental status and preterm birth

Compared with periodontitis, dental caries—as a localized, non-destructive lesion—has shown a weaker and less consistent association with adverse pregnancy outcomes, including preterm birth (PTB). A comprehensive 2018 systematic review and meta-analysis by Wagle et al. evaluated observational studies from multiple countries. They concluded that dental caries alone was not associated with an increased risk of PTB, nor was there a meaningful difference in PTB rates between women with treated versus untreated carious lesions [242]. Similar conclusions were reported in regional analyses from Asia and Sub-Saharan Africa, which found that caries often coexisted with socioeconomic disadvantage or poor overall maternal health but did not independently predict PTB after adjustment for confounders [243,244].

However, advanced caries-related pathology, particularly apical periodontitis and chronic endodontic infections, may be more relevant to PTB risk because of their capacity to generate persistent systemic inflammation. A 2021 systematic review by Jakovljević et al. synthesized evidence from nine studies and found a possible association between maternal apical periodontitis and PTB, low birth weight, and preeclampsia, although the included studies were methodologically heterogeneous and often lacked rigorous periodontal or obstetric characterization [245]. The review emphasized that apical periodontitis should be conceptualized as a chronic inflammatory focus—similar in biological effect to periodontitis—capable of producing systemic inflammatory mediators, bacteremia, and maternal immune activation, all of which are plausible mechanistic pathways implicated in PTB.

More recent cohort studies support this emerging perspective. A 2022 Finnish population-based study (N = 24,000) reported that women with untreated apical periodontitis had higher rates of systemic inflammatory markers and slightly increased risk of PTB. However, the association was attenuated after adjusting for socioeconomic and behavioral factors [246]. In addition, a 2023 Japanese cohort study demonstrated that periapical lesions with radiographic signs of chronic infection were independently associated with elevated serum CRP levels during pregnancy—a biomarker repeatedly linked to higher PTB risk [247].

Although the evidence remains less robust than that for periodontitis, the current literature suggests that chronic apical infections—rather than caries itself—may contribute to PTB through sustained low-grade inflammation, episodic bacteremia, and dysregulation of the maternal–fetal immune interface. High-quality prospective studies with standardized definitions of dental pathology and obstetric outcomes are needed to confirm these associations.

### 1.3.3 Global oral health status and utilization of dental care

Beyond specific diseases, several recent studies have examined overall oral health status—including self-reported gum bleeding, tooth loss, poor oral hygiene, and lack of dental visits—as markers of increased risk of PTB. Adebayo et al. reviewed the association between oral diseases and adverse pregnancy outcomes. They reported that while caries alone was not consistently linked to PTB, poor oral hygiene, gingival bleeding, and advanced periodontal disease were associated with low birth weight and preterm delivery in several African cohorts [248].

Large administrative datasets, such as the Taiwanese national database analyzed by Lee et al. show that greater severity of diagnosed periodontal disease correlates with progressively higher PTB risk, and that women who had received periodontal treatment before or early in pregnancy tended to have lower PTB rates than those who remained untreated. These findings support the idea that "oral health status" is not only a reflection of local disease but also a proxy for chronic inflammation and access to preventive care [249].

Surveys from developed countries consistently indicate that only a minority of pregnant women attend dental care during pregnancy, often due to misconceptions that dental treatment is unsafe, a lack of referral from obstetric providers, or financial barriers. Large national surveys from the United States, United Kingdom, Australia, and Scandinavia report that only 30–50% of pregnant women receive any oral health-related care during pregnancy, despite clinical guidelines supporting its safety and necessity [250-254].

Their knowledge of its importance may influence the extent to which women neglect oral health during pregnancy. Recent surveys from high-income countries show that many pregnant women do not recognize oral health as a factor that could protect and keep their fetus safe. This misunderstanding contributes to low dental-care utilization during pregnancy [255]. However, this may be due to a lack of awareness that oral health is correlated with children's health, a pattern consistently observed in population-based surveys from the United States, the United Kingdom, and Australia [256,257].

According to Dahlen et al. [258], dental attendance during pregnancy remains low, with only about one-third of pregnant women receiving any dental care and less than half seeking care even when experiencing dental problems or emergencies. More recent data confirm these findings: national surveys from the U.S. and Europe report that only 30–50% of pregnant women receive any dental care during pregnancy, indicating persistent gaps in knowledge and awareness about oral health during pregnancy [259]. This is due to the limited availability of accessible, patient-friendly information provided by professional organizations such as the American Dental Association and the American College of Obstetricians and Gynecologists. These organizations offer only brochures and limited written materials, and although they endorse dental care during pregnancy, many women remain unaware of these recommendations [260]. However, there are still no comprehensive, universally implemented clinical guidelines that must be followed for all pregnant dental patients,

and awareness of existing policies is low among both patients and providers [261]. This is an issue because many women rely on these organizations and trust them to provide all necessary information. Still, without adequate counseling by healthcare professionals, women are not receiving the information they need. This causes fewer women to understand the severity of dental visits and oral health care during pregnancy, contributing to persistently low utilization rates worldwide [262].

### 1.4 The Mechanism of Oral-Preterm Association

The association between periodontal disease and preterm birth (PTB) has been extensively studied due to the central role of inflammation in initiating normal and pathological labor [27,p. 769]. Periodontal disease is a chronic infectious and inflammatory condition that can influence systemic physiology through bacteremia, inflammatory cytokine release, immune activation, and molecular mimicry pathways [32,p. 30]. These processes align with established mechanistic models of spontaneous PTB, which emphasize infection, inflammation, decidual activation, uterine contractility, and cervical ripening as core biological pathways [29,p. 56]. Current evidence highlights four major mechanistic pathways linking periodontal disease to adverse pregnancy outcomes: bacterial dissemination, dysregulation of systemic inflammatory mediators, maternal immune responses, and molecular mimicry involving antiphospholipid antibodies [35,p. 861].

#### 1.4.1 Bacteria spread and infection of distal tissues

Periodontal disease is driven by Gram-negative anaerobes such as *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythia*, *P. intermedia*, *T. denticola*, and *C. rectus* [234,p. 720]. In moderate to severe disease, the ulcerated pocket epithelium can reach up to 20–70 $cm^2$, thereby providing direct access for pathogens and virulence factors to enter the bloodstream and disseminate systemically, particularly during routine oral activities such as chewing, flossing, and toothbrushing [263].

Animal studies provide strong causal evidence. Collins et al. showed that experimental *P. gingivalis* infection in pregnant hamsters resulted in reduced fetal weight and increased fetal mortality [263,p. 4350]. Han et al. demonstrated that systemic inoculation with *F. nucleatum* in pregnant mice leads to preterm labor and stillbirth, with the pathogen invading placental vasculature [236,p. 556]. Yeo et al. [264] confirmed that C. rectus exposure induces fetal growth restriction and placental colonization in murine models.

Human studies corroborate these findings. Periodontal pathogens (*F. nucleatum*, *P. gingivalis*, *C. rectus*, *T. forsythia*) have been cultured or identified by PCR in amniotic fluid, placenta, and fetal membranes of women with preterm birth [264,p. 1991]. Mitchell-Lewis et al. observed elevated levels of *T. forsythia* and *C. rectus* in mothers of preterm low-birth-weight infants [263,p. 4350]. Cases of stillbirth linked to maternal *F. nucleatum* bacteremia reinforce the biological plausibility of transplacental spread [35,p. 861].

#### 1.4.2 Periodontal inflammation and altered inflammatory mediator levels

Normal labor is characterized by a progressive rise in proinflammatory mediators—including IL-1β, IL-6, TNF-α, and prostaglandin $E_2$ ($PGE_2$)—toward term [116,p. 1234]. Periodontal disease elevates systemic levels of these cytokines, thereby accelerating inflammatory signaling and potentially triggering premature uterine contractions [263,p. 4350]. Elevated $PGE_2$ levels derived from inflamed periodontal tissues have been linked to preterm labor and low birth weight [234,p. 720].

Maternal systemic inflammation markers support this mechanism. Elevated C-reactive protein (CRP) in early pregnancy is associated with increased PTB risk [116,p. 1234]. Inflammatory mediators measured in gingival crevicular fluid (IL-1β, TNF-α, $PGE_2$) have been associated with preterm birth in observational cohort studies [265]. Lipopolysaccharide (LPS) from periodontal pathogens activates TLR-2 and TLR-4, thereby inducing uterine contractility and matrix degradation, which contribute to cervical ripening and PPROM [265,p. 420].

#### 1.4.3 Maternal acquired immune response to oral pathogens

Emerging evidence links periodontal disease with autoimmune mechanisms relevant to APS. APS is characterized by antiphospholipid antibodies (including $\beta_2$-glycoprotein I–dependent antibodies) that promote placental thrombosis, infarction, and preterm birth [120,p. 82]. Molecular mimicry between $\beta_2$GPI and peptide sequences of P. gingivalis and A. actinomycetemcomitans may induce cross-reactive antibodies [121,p. 2241]. These antibodies can disrupt trophoblast anticoagulant mechanisms and promote placental vascular injury [122,p. 411]. Experimental studies show that antibodies generated against periodontal pathogens cross-react with $\beta_2$GPI and induce fetal resorption and growth restriction in animal models [265,p. 420].

### 1.5 Fusobacterium nucleatum and Preterm Birth

The international literature thus converges on F. nucleatum as a biologically plausible mediator linking maternal periodontal disease to preterm birth, supported by consistent clinical associations, strain-level oral–placental concordance, and robust animal models.

Fusobacterium nucleatum is a Gram-negative, anaerobic oral commensal and periodontal pathobiont that has been increasingly implicated in adverse pregnancy outcomes, including preterm birth, stillbirth, and neonatal sepsis. Historically considered part of the subgingival biofilm, F. nucleatum is now recognized as a “bridge” organism that links early and late colonizers in dental plaque and can disseminate hematogenously to extraoral sites, including the placenta and amniotic cavity. Intrauterine infection is estimated to contribute to 30–40% of spontaneous preterm births, and F. nucleatum is among the most frequently detected microorganisms in placental and amniotic samples from such cases.

#### 1.5.1 Epidemiological and clinical evidences

Clinical and molecular studies have repeatedly demonstrated an association between Fusobacterium nucleatum and preterm birth (PTB) within the broader context of infection- and inflammation-mediated pathways [235,p. 861]. Case reports and small series have identified F. nucleatum in amniotic fluid, placental tissue, and fetal compartments of women presenting with preterm labor, chorioamnionitis, and stillbirth, sometimes in the absence of classical genital-tract pathogens [266-270]. Culture-independent techniques, including 16S rRNA gene sequencing and species-specific PCR, have confirmed that F. nucleatum is detectable in a substantial proportion of intrauterine infections associated with PTB [270,p. 32]. These molecular studies suggest that F. nucleatum may account for a significant fraction of infection-related preterm births, particularly at earlier gestational ages, when infectious etiologies are more common [270,p. 32].

Strain-level and metagenomic analyses indicate that F. nucleatum identified in the placenta and fetal compartment often shows close genetic relatedness to oral rather than vaginal strains, supporting an oral–hematogenous route of transmission [270,p. 32]. Studies integrating oral and placental microbiome profiling demonstrate concordance between maternal oral communities enriched in F. nucleatum and placental taxa in PTB cases [266,p. 45].

Epidemiologically, observational studies in diverse populations have linked maternal periodontitis and oral dysbiosis, including increased abundance of F. nucleatum, to an increased risk of PTB and low birth weight [266,p. 45]. Global meta-analyses of periodontal disease and adverse pregnancy outcomes consistently report an elevated risk of PTB among women with periodontitis, and highlight F. nucleatum and other anaerobic Gram-negative species as key taxa in this association [266,p. 45].

In studies from low- and middle-income settings, including Sub-Saharan Africa and Asia, higher prevalence and relative abundance of F. nucleatum in subgingival plaque or saliva have been observed among mothers of preterm or low-birth-weight infants compared with term controls, even after adjustment for clinical periodontal status and sociodemographic factors [266,p. 45].

Recent narrative and scoping reviews of pregnancy microbiome research indicate that publications explicitly addressing “Fusobacterium” and “preterm birth” have increased rapidly, integrating findings from the oral, vaginal, and placental microbiomes with clinical epidemiology [270,p. 32]. Not all studies detect F. nucleatum in every case of preterm birth, which is consistent with the multifactorial nature of PTB and the involvement of multiple microbial and non-microbial pathways. [237,p. 103]. However, several placental and chorioamniotic membrane studies indicate that F. nucleatum is disproportionately enriched in tissues from preterm or stillborn pregnancies compared with term controls, especially in the presence of histologic chorioamnionitis or dense echogenic material (“amniotic sludge”) [270,p. 32]. Taken together, clinical, molecular, and epidemiologic data support the view that F. nucleatum is an important—though not exclusive—microbial contributor to infection-driven preterm birth [270,p. 32].

### 1.5.2 Experimental and animal studies

Robust experimental evidence from animal models has clarified the causal potential of F. nucleatum and other oral pathogens in adverse pregnancy outcomes [270,p. 32]. In classic models, systemic inoculation of pregnant animals with periodontal pathogens such as Porphyromonas gingivalis and Campylobacter rectus has been shown to induce placental inflammation, fetal growth restriction, fetal loss, and preterm delivery [263,p. 4350]. Building on these observations, murine models using F. nucleatum demonstrate that intravenous or hematogenous introduction of the organism leads to placental colonization, preterm labor, and fetal death. At the same time, systemic infection in other maternal organs remains relatively limited [270,p. 32].

Experimental studies indicate that F. nucleatum elicits a strong placental inflammatory response characterized by leukocyte infiltration, decidual necrosis, and elevated pro-inflammatory cytokines, consistent with Toll-like receptor (TLR)-mediated activation [270,p. 32]. These models suggest a predominant role for TLR4 signaling in mediating placental injury and fetal demise following F. nucleatum exposure, although TLR2 and other pattern recognition receptors may also contribute [270,p. 32].

Additional mouse studies employing different F. nucleatum strains, doses, and routes of administration have reproduced a spectrum of outcomes, including preterm birth, intrauterine growth restriction, and stillbirth, thereby reinforcing the robustness of these findings [270,p. 32]. Experimental work has demonstrated a marked tropism of F. nucleatum for the placenta, mediated in part by adhesins such as FadA and other outer-membrane proteins that bind host molecules, including E-cadherin and Gal-GalNAc, on endothelial and trophoblast cells [270,p. 32].

More recent mechanistic studies indicate that virulence factors such as FadA and Fap2 not only facilitate adhesion and invasion but also modulate local immune responses and vascular integrity at the maternal–fetal interface [269,p. 136].
Collectively, these experimental data provide substantial proof of principle that hematogenous dissemination of oral bacteria, particularly F. nucleatum, can directly infect the placenta and trigger inflammatory cascades sufficient to cause preterm birth and fetal demise, supporting the biological plausibility of associations observed in human studies [235,p. 861].

### 1.5.3 Proposed mechanisms linking F. nucleatum to preterm birth

Several complementary mechanisms have been proposed to explain how *F. nucleatum* contributes to spontaneous preterm birth within the broader framework of infection- and inflammation-related pathways [29,p. 56]. Central to current models is hematogenous translocation from the maternal oral cavity, whereby periodontitis and routine oral activities, such as toothbrushing or dental procedures, can induce transient bacteremia, allowing F. nucleatum to enter the systemic circulation [263,p. 4350].

Once at the maternal–fetal interface, F. nucleatum adheres to and invades endothelial and trophoblast cells through virulence factors such as FadA and outer-membrane proteins, including Fap2, which interact with host receptors such as E-cadherin and Gal-GalNAc [267,p. 112].

Within placental tissue, F. nucleatum activates innate immune pathways, primarily involving TLR4 and downstream NF-κB signaling, leading to increased production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and chemokines [270, p. 32]. This inflammatory cascade promotes neutrophil infiltration, decidual necrosis, endothelial damage, and disruption of placental structure and function, changes that are consistent with histological chorioamnionitis and placental dysfunction in PTB. [270,p. 32].

In vitro studies show that F. nucleatum and its lipopolysaccharide stimulate trophoblasts, decidual cells, and endothelial cells via TLR2/TLR4-dependent and partially TLR-independent pathways, inducing cytokines and matrix metalloproteinases that may weaken fetal membranes and enhance uterine contractility [165,p. 360]. Emerging data from microbiome and immunology research suggest a dose- and context-dependent effect, in which a very low-level presence of F. nucleatum may be transient or immunomodulatory, whereas higher bacterial loads or a dysbiotic community drive pathological inflammation and tissue damage [237,p. 103].

Host factors—including maternal immune status, metabolic and cardiovascular comorbidities, environmental exposures, and genetic susceptibility—further modify the host response to oral and placental colonization with F. nucleatum and other periodontal pathogens [270,p. 32].

Overall, current evidence supports a model in which F. nucleatum, most likely originating from the maternal oral cavity, reaches the placenta via the bloodstream, adheres to and invades placental tissues through specific adhesins, activates TLR-driven inflammatory pathways, and contributes to chorioamnionitis, membrane weakening, placental dysfunction, and the clinical syndrome of spontaneous preterm birth [270,p. 32].

### 1.6 Existing Antenatal Care Models to Reduce Preterm Birth

Over the past two decades, international strategies to prevent preterm birth have increasingly focused on strengthening antenatal care (ANC) as a platform for early risk identification, prevention, and timely management of complications [271–273]. The 2016 WHO guideline on antenatal care for a positive pregnancy experience recommends a minimum of eight ANC contacts, replacing earlier four-visit "focused ANC" models after evidence showed that fewer contacts were associated with higher perinatal mortality [275]. The updated model emphasizes respectful, person-centred care and bundles of effective interventions, including routine nutritional supplementation (iron–folic acid, context-specific calcium), blood pressure and urine screening, early ultrasound before 24 weeks to improve gestational age dating, screening and management of infections and structured counselling on healthy diet, physical activity, tobacco and alcohol cessation, and birth preparedness [276,277]. These elements are now being adopted, with adaptations, in many low-, middle-, and high-income countries as the foundation for primary prevention of adverse pregnancy outcomes, including preterm birth [278].

Beyond general ANC content, global guidelines increasingly address targeted prevention in women at increased risk of spontaneous preterm birth [279,280]. The

WHO recommendations on interventions to improve preterm birth outcomes, together with regional and national guidelines, highlight a set of key strategies: accurate gestational age assessment with early ultrasound; systematic risk assessment based on previous preterm birth, multiple gestation, uterine anomalies, or short cervical length; and use of vaginal progesterone or cervical cerclage in selected high-risk women [281, 282]. The NICE guideline NG25 (UK) and the ACOG Practice Bulletin No. 234 (USA) both recommend transvaginal cervical-length screening in women with a history of spontaneous preterm birth or other risk factors, followed by vaginal progesterone or cerclage when cervical shortening is confirmed, while also encouraging optimization of modifiable factors such as smoking cessation, interpregnancy interval, weight management, and treatment of specific infections [283-285]. Although details differ between countries, for example, in the extent of cervical-length screening or choice of progesterone formulation, comparative reviews of clinical practice guidelines show broad agreement on these core interventions for secondary prevention [286,287].

When preterm birth becomes imminent, current strategies focus on tertiary prevention—reducing neonatal mortality and morbidity rather than preventing the timing of birth itself [288]. WHO and national guidelines converge on a package that includes antenatal corticosteroids for women at risk of birth before about 34 weeks (with updated criteria to ensure adequate gestational age assessment, absence of maternal infection, and availability of appropriate neonatal care), intravenous magnesium sulfate for fetal neuroprotection in very early gestations, short-term tocolysis to allow completion of steroid courses and in-utero transfer, prophylactic antibiotics for preterm prelabour rupture of membranes (PPROM), and delivery in facilities with suitable neonatal intensive care [289-291].For the newborn, recommendations emphasise delayed cord clamping, early continuous positive airway pressure (CPAP) where needed, prevention of hypothermia, and kangaroo mother care for clinically stable preterm infants, which has been shown to improve survival and long-term outcomes [292-294]. Despite these advances, implementation remains uneven: many low- and middle-income settings struggle with shortages of trained staff, limited access to ultrasound, progesterone, or neonatal intensive care, and gaps in coverage of the WHO 2016 ANC contact schedule [295-297]. Consequently, current global priorities stress not only the technical content of guidelines, but also health-system strengthening and equity-focused implementation to ensure that evidence-based preventive strategies for preterm birth are accessible to all women and infants, particularly in high-burden regions [298-300].

Routine oral health screening during pregnancy is formally integrated into antenatal care (ANC) in several countries, where national or regional guidelines recommend that obstetricians and gynecologists assess a woman’s oral health at the first prenatal visit and encourage dental check-ups early in pregnancy [301-303]. Professional bodies such as the American College of Obstetricians and Gynecologists (ACOG) and the American Dental Association (ADA) now state that preventive, diagnostic, and restorative dental treatment is safe throughout pregnancy and should not be delayed based on gestational status [304-306]. They recommend assessing oral health at the first prenatal visit, reassuring women about the safety of dental care, and

actively referring those with dental problems or periodontal disease for treatment [307-309]. A U.S. interprofessional consensus statement and subsequent state-level practice guides (e.g., the Texas "Smiles for Moms and Babies" program) provide structured recommendations for obstetric and dental providers, including brief chairside oral health screening, counselling on tooth-brushing with fluoride toothpaste and sugar reduction, and systematic referral pathways to dentists for pregnant women, particularly those with low income or limited access to care [310-312]. Public-health initiatives, such as the CDC–AAP "Protect Tiny Teeth" campaign, further encourage obstetricians, midwives, and pediatricians to discuss oral health during pregnancy and early infancy and to dispel myths that dental treatment is harmful in pregnancy [313-315].

In Australia, national Pregnancy Care Guidelines include a dedicated section on oral health, recommending that ANC providers routinely ask about dental symptoms, give preventive advice, and refer pregnant women—especially those with visible disease or low socioeconomic status—for dental assessment; midwives are increasingly trained through programs such as the Midwifery Initiated Oral Health (MIOH) education model to perform simple oral screening and provide referrals [316-318]. In Europe, the European Federation of Periodontology and national societies (e.g., British Society of Periodontology) advise that non-surgical periodontal therapy during pregnancy is safe and improves periodontal status, while emphasizing that optimal timing for periodontal treatment may be before conception in women with known disease [319-321]. Canada, the UK, and several other countries have issued public health guidance for pregnant women that emphasizes maintaining good oral hygiene, regular dental check-ups, smoking cessation, and limiting free sugars, and encourages ANC providers to include oral health messages in routine counselling [322-324].

In Japan, antenatal and perinatal oral-health practices are increasingly embedded within broader maternal and child health frameworks [325-327]. For example, the national document *"From Pregnancy through to Child-Rearing in Japan – Guide"* published by the Ministry of Health, Labour and Welfare includes dental check-ups, tooth-brushing guidance, and nutritional counselling for mothers and young children as part of the municipal health check-ups during pregnancy and infancy [328-329]. Studies in Japanese settings show that early oral health intervention—such as an education programme for pregnant women before 20 weeks of gestation that includes a "toothpick brushing method"—significantly improved self-assessed periodontal symptoms (OR = 3.8) and reduced Candida counts in saliva by late pregnancy [330-332].

In Saudi Arabia, the Ministry of Health issues public recommendations on "Oral and Dental Health of Pregnant Women," advising that dental hygiene should receive special attention during pregnancy, that dental care is safe with appropriate precautions, and that pregnant women should maintain regular dental visits and good oral-hygiene practices [333-335]. Recent studies from Saudi Arabia show that researchers and policymakers explicitly frame oral health care as an integral component of prenatal care, and call for prenatal providers to routinely ask about oral

symptoms, inspect the mouth, and refer women to dentists; they also emphasize the need to integrate dental services more effectively into primary maternal-care settings [336,337]. However, utilization data indicate that many pregnant women in Saudi Arabia still do not receive dental care during pregnancy, underscoring a significant implementation gap [338,339].

China has implemented several large-scale public health initiatives that indirectly strengthen oral health during pregnancy [340-342]. For example, the National Oral Health Comprehensive Intervention Program for Children and Adults emphasizes oral-health education for women of reproductive age and includes pregnancy-focused materials [343,344]. Provincial Maternal and Child Health Hospitals (e.g., in Beijing, Shanghai, Guangdong) increasingly recommend first-trimester oral-health assessment, counselling on periodontal disease, and referral to dental services as part of standardized maternal health management packages [345,346]. In Sri Lanka, a national programme (starting around 2009) integrated oral-health awareness, screening and referral into antenatal services in low-income, urban pregnant women; for example, pregnant mothers were screened at antenatal clinics and referred to nearby dental clinics, with education sessions delivered in local languages, and screening coverage increased from ~59% to ~77% in a pilot period [347-349].

In Kazakhstan, antenatal care (ANC) coverage is among the highest in the region, with more than 95% of women receiving at least four ANC visits and almost all births attended by skilled personnel [350-352]. National policy, as reflected in the WHO SRMNCAH policy survey, recommends at least eight ANC contacts, aligning with the 2016 WHO model and ensuring early registration (before 12 weeks) and continuous follow-up through primary health-care organizations [353-355]. However, a review of publicly available Kazakh legislation, clinical protocols and policy summaries shows no explicit requirement for routine oral-health screening within ANC, and the 2022 WHO Oral Health Country Profile for Kazakhstan reports no national oral-health policy or strategy, even though basic oral screening and restorative care are available at the primary-care level [356-358]. Similar patterns are seen across Central Asia: regional analyses describe substantial progress in maternal-health coverage and updated obstetric protocols in Kazakhstan, Kyrgyzstan, Tajikistan and Uzbekistan, but oral health is rarely mentioned as a structured component of perinatal care packages [359-361]. At the same time, WHO estimates indicate a high burden of untreated dental caries and severe periodontal disease in Kazakhstan, and local research—including a Kazakh systematic review and a case–control analysis—has shown that periodontitis is associated with increased odds of preterm birth, especially extremely and very preterm birth [362-364]. In contrast to countries such as the United States, Australia, and Japan, where ANC guidelines or professional statements explicitly recommend dental assessment and referral during pregnancy, Central Asian health systems have not yet systematically integrated oral health promotion, screening, and periodontal management into national ANC protocols [365-367]. This gap is significant for Kazakhstan, where high ANC coverage provides a strong platform for implementing low-cost oral health interventions that could help reduce the burden of periodontitis and potentially lower preterm birth rates [368-370].

Evidence shows that routine antenatal oral check-ups improve pregnancy outcomes through several mechanisms [371]. First, early detection and treatment of periodontal disease reduces local inflammation and bacterial load, decreasing systemic inflammatory mediators—such as IL-6 and TNF-α—implicated in triggering preterm labor [372]. Studies in Japan and the U.S. demonstrate that periodontal treatment during pregnancy significantly improves periodontal status and reduces oral pathogen burden [373]. Second, routine check-ups identify dental caries, abscesses, and gingival infections, which, if left untreated, may progress and contribute to maternal systemic inflammation or bacteremia [374]. Third, counseling provided during these visits improves maternal knowledge, toothbrushing behavior, fluoride use, and dietary patterns, all of which are independently associated with better maternal oral health [375]. Finally, integrated programs (e.g., U.S. Medicaid perinatal dental benefits, Australia's MIOH model) increase dental care utilization among low-income women, who are at the highest risk for both periodontal disease and adverse pregnancy outcomes [376].

Although persistent gaps remain in many regions, international evidence indicates that systems in which oral check-ups are routinely integrated into ANC services demonstrate better maternal oral health indicators, lower rates of untreated periodontal disease, and potentially reduced risks of preterm birth and low birth weight, especially among socioeconomically vulnerable populations [377]. However, a systematic appraisal of antenatal oral health guidelines found that, although many statements now recommend that ANC providers discuss oral health, perform basic screening, and refer to dental services, there is wide variability in guideline methodological quality and in the specificity of recommended practices [378]. Surveys from Australia and other settings show that midwives and ANC providers often feel insufficiently trained, lack clear local protocols, and face barriers such as limited consultation time, high dental costs for patients, and persistent misconceptions about the safety of dental procedures in pregnancy [379]. International experience indicates a growing consensus that oral health promotion, early identification of periodontal disease, and timely dental care should be routine components of comprehensive antenatal care, but also highlights the need for better provider training, clearer referral pathways, and integration of oral health into national ANC packages—particularly in low- and middle-income countries where both periodontal disease and preterm birth are highly prevalent [380].

## 2 MATERIAL AND METHODS

### 2.1 Estimated scope and structure of research

The study was conducted in three sequential phases, combining systematic evidence synthesis with observational epidemiology to investigate maternal and oral-health–related determinants of spontaneous preterm birth (sPTB) in Kazakhstan.

Preparatory Phase – Systematic Review and Meta-analysis

An extensive literature search was conducted to synthesize evidence on the association between oral diseases and preterm birth. Major databases—including PubMed, Scopus, Web of Science, Cochrane Library, eLibrary, and local Kazakh databases—were systematically searched using MeSH terms such as *"periodontal disease AND preterm birth," "dental caries AND preterm birth,"* and *"periapical infection AND preterm birth."* After removing duplicates, titles and abstracts were screened, and full texts of eligible studies were reviewed [29]. High-quality studies meeting the inclusion criteria were incorporated into a random-effects meta-analysis to derive pooled effect estimates and inform the analytic framework for subsequent empirical phases.

Phase I – Cohort study

A multicenter hospital-based cohort of 3,000 pregnant women, recruited from perinatal centers in Atyrau, Aktobe, and Kyzylorda between September 2022 and April 2024. Eligible participants were singleton pregnancies with informed consent, and the study had clear inclusion and exclusion criteria.

Participants completed a structured survey, and clinical data were extracted from the medical record system. Follow-up continued until delivery. After removal of incomplete or duplicate records, 2,235 women were included in the final cohort. Among them, 280 had preterm births (PTB), and 1,195 had term births (TB). The cohort dataset included demographic characteristics, obstetric history, socioeconomic indicators, self-reported health status, and pregnancy complications. This phase identified maternal demographic, medical, obstetric, socioeconomic, and behavioral risk factors associated with preterm birth in the population[27].

Phase II – Nested matched case–control study

Within the cohort, a nested matched case–control study was conducted among 270 women, including 90 cases of spontaneous preterm birth and 180 gestational-age–matched term controls[28]. This phase examined whether oral health status and the presence of the oral pathogen Fusobacterium nucleatum in maternal saliva and placental tissue were associated with increased risk of sPTB. Clinical periodontal assessments and molecular diagnostics (qPCR) were used to evaluate oral infection as a potential biological contributor to preterm birth. Statistical modeling and machine-learning prediction algorithms (including multivariable logistic regression, decision trees, and stacking models) were applied to evaluate independent associations and identify high-risk phenotypes.

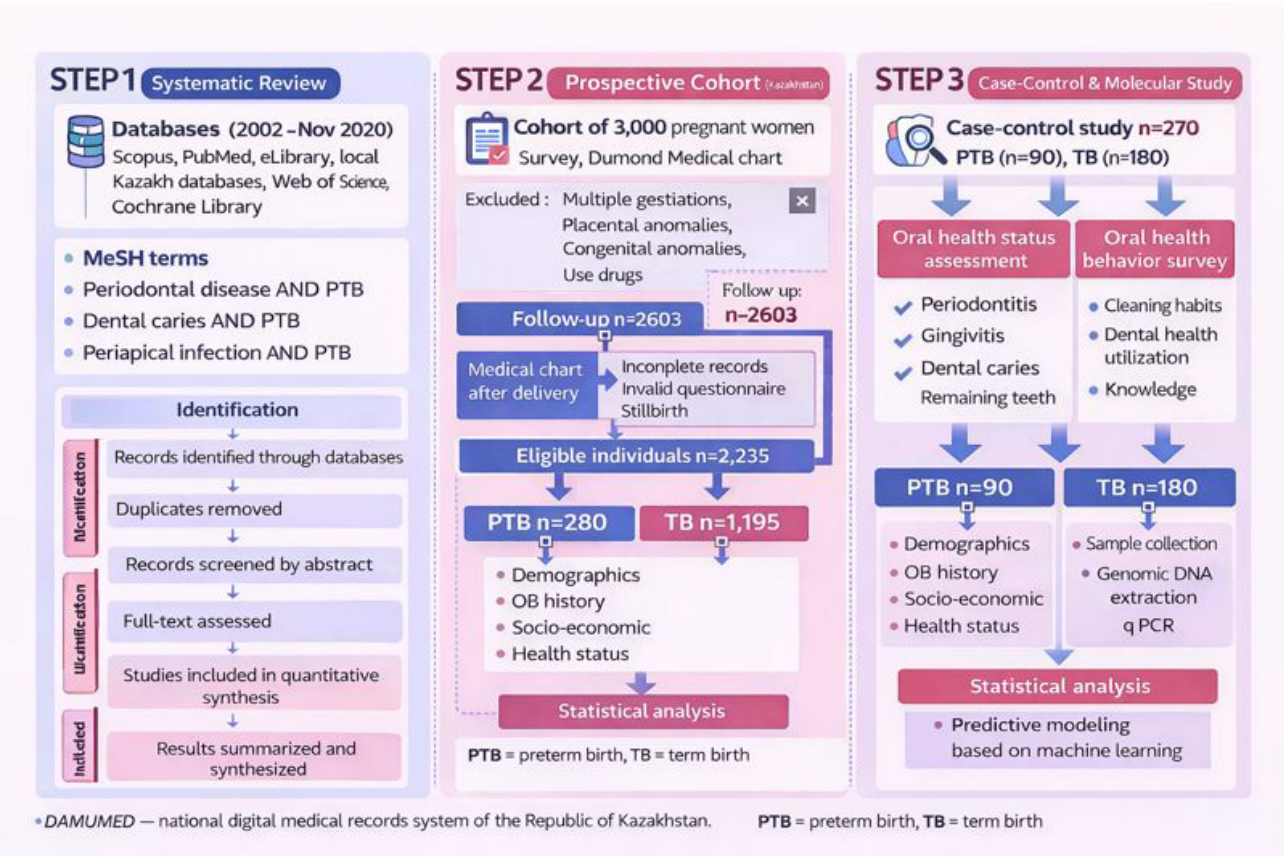


Figure 1 – The schematic diagram of the research design

## 2.2 Research Methods of Systematic Review and Meta-Analysis

2.2.1 Study design and reporting framework

This systematic review and meta-analysis were conducted in accordance with the internationally recognized methodological standards outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [381] and the Cochrane Handbook for Systematic Reviews of Interventions [382]. Although the review protocol was not prospectively registered in PROSPERO, the complete protocol, including eligibility criteria, analytical approach, and the full PRISMA checklist, was provided to ensure methodological transparency, reproducibility, and adherence to best practices. The overarching research question guiding this review was whether pregnant individuals affected by oral diseases, such as periodontal disease, dental caries, or apical periodontitis are at increased risk of preterm birth compared with those with healthy oral conditions.

2.2.2 Search strategy and information sources

A comprehensive and systematic search of the scientific literature was conducted through 20 November 2022, using multiple major electronic databases to ensure complete coverage of published research. Databases included Scopus, PubMed/MEDLINE, Web of Science, eLibrary, regional databases, and the Cochrane

Library. The search strategy was structured using combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to oral diseases, pregnancy, and adverse outcomes. Key search terms included: *"Periodontal disease"*, *"Periodontitis"*, *"Dental caries"*, *"Oral disease"*, *"Apical periodontitis"*, paired with *"pregnancy"*, *"preterm birth"*, *"adverse pregnancy outcomes"*, and *"low birth weight"*. Boolean operators (AND/OR), truncations, and database-specific filters were applied to maximize sensitivity and specificity. Reference lists of eligible articles and relevant reviews were manually screened to identify additional studies not captured by electronic searches.

2.2.3 Study selection process

The study selection process adhered to PRISMA guidelines for transparent reporting. Two independent reviewers screened all retrieved records in a two-stage process. Initially, titles and abstracts were screened to identify potentially relevant studies. Full texts of articles meeting the preliminary criteria were then retrieved and assessed in detail against prespecified inclusion and exclusion criteria. Observational studies evaluating pregnant women with clinically assessed oral health status and reporting preterm birth and/or low birth weight outcomes were included. Exclusion criteria comprised reviews, meta-analyses, case reports, case series, conference abstracts, experimental animal studies, and articles lacking relevant outcomes. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer. The final selection process is visually represented in the PRISMA flow diagram (figure 2), illustrating the number of articles identified, screened, excluded, and ultimately included [29,p. 56].

2.2.4 Eligibility criteria

The review included observational studies (cohort, case-control, and cross-sectional designs) of pregnant women in which oral health status was assessed clinically or radiographically. Eligible studies were required to report at least one of the following outcomes: preterm birth (PTB) or low birth weight (LBW). Diagnostic definitions for oral diseases had to be explicitly stated. Studies focusing exclusively on nonpregnant populations, laboratory assays, or periodontal treatment interventions were excluded. Only articles published in peer-reviewed journals in English or Russian were considered.

2.2.5 Data extraction and management

Data extraction was conducted independently by two trained reviewers using a standardized and piloted data extraction form. Extracted variables included study characteristics (author, year of publication, country, study design, and sample size), diagnostic criteria for periodontal disease, dental caries, or apical periodontitis, outcome definitions, measured confounders, and the effect estimates reported (odds ratios or risk ratios with corresponding 95% confidence intervals). Where necessary, authors were contacted for clarification or additional data. The extracted data were

cross-checked for accuracy and completeness prior to analysis.The methodological quality of included studies was appraised using two validated tools: the Newcastle–Ottawa Scale (NOS) for cohort and case-control studies and the ROBINS-I tool for non-randomized studies. Each study was evaluated for selection bias, comparability of study groups, exposure and outcome assessment, and completeness of follow-up. Studies were classified into low-, moderate-, or high-risk-of-bias categories. Risk-of-bias assessments were performed independently by two reviewers, with discrepancies resolved through discussion.

2.2.6 Statistical analysis

All statistical analyses were carried out using Review Manager 5.4. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model (DerSimonian–Laird method) to account for between-study heterogeneity. Statistical heterogeneity among studies was quantified using the $I^2$ statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Sensitivity analyses were performed by sequentially excluding individual studies to assess the influence of each study on the pooled estimates. Subgroup analyses were conducted by oral disease type (periodontitis, dental caries, apical periodontitis) and study design, where sufficient data were available. Publication bias was assessed by visual inspection of funnel plots and, where applicable, by the Egger regression test.

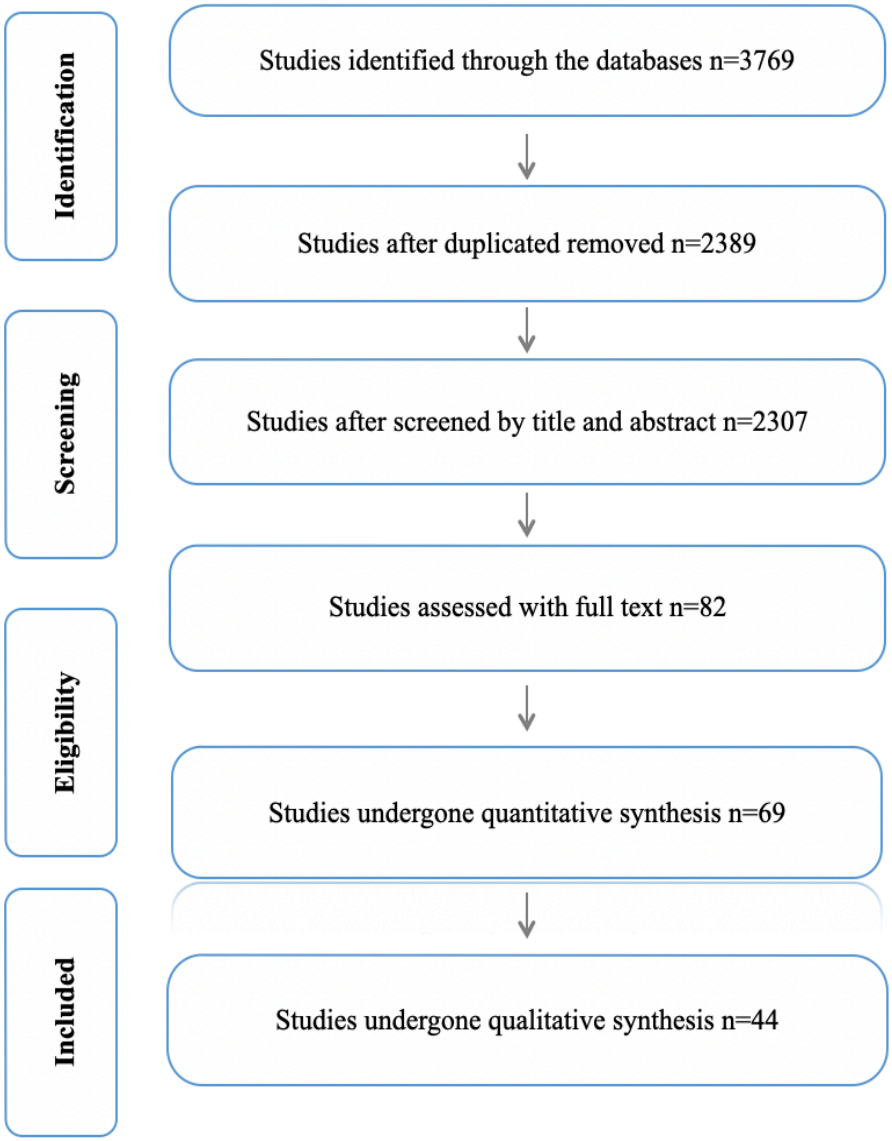


Figure 2 – PRISMA Flow Diagram Illustrating the Study Selection Process

## 2.3 Research Methods of Cohort Study

2.3.1 Study population

Pregnant women registered in local perinatal centers in the Atyrau, Aktobe, and Kyzylorda regions were invited to participate in the cohort study. The structured questionnaire was distributed to all pregnant women attending antenatal care during the recruitment period (September 2022 – April 2024), before delivery and before pregnancy outcomes were known.

Minimum sample size: For analyzing multiple risk factors in a cohort (e.g., maternal socioeconomic, clinical, and lifestyle factors) consider a estimated relative risk of 1.5, with a 10% preterm birth rate in the non-exposed group, and assuming 80%

power and a 5% significance level, the minimum sample size required for each group (exposed and non-exposed) is approximately 335 participants.

Before administering the questionnaire to the main study population, a trained researcher fluent in Kazakh and Russian conducted a pilot survey among 30 pregnant women at the Aktobe Reproductive and Perinatal Center to improve clarity and ensure cultural and linguistic appropriateness of the items.

A total of 3000 questionnaires were collected during antenatal visits. After delivery, the final participant inclusion was determined a reviewing medical records, ensuring that only women who met the eligibility criteria and had complete obstetric data were retained. After excluding ineligible, incomplete, or duplicate responses, 2,235 valid questionnaires were included in the final analysis.

Inclusion criteria: women with a singleton pregnancy.

Exclusion criteria: women with multiple pregnancies (twins, triplets, etc.), with severe pregnancy complications such as placenta previa, placental abruption, or congenital or structural fetal anomalies diagnosed before inclusion in the study, use of immunosuppressive or anti-inflammatory drugs, with incomplete medical records, or with incomplete or duplicate questionnaires identified after collection.

2.3.2 Research instruments and sample collection

Included both clinical and self-reported data. Before delivery, pregnant women completed a structured questionnaire designed to assess maternal factors, including socioeconomic status, lifestyle habits, and oral health care utilization. Participants could choose the mode of completion (online or offline) based on availability and convenience. The questionnaire also included items on self-reported oral health status, such as common oral symptoms (gum bleeding, tooth pain, tooth mobility, halitosis, caries, tooth for extraction) and frequency of dental visits. The online survey was administered via a secure platform, and participation was voluntary; paper-based questionnaires were manually entered into the same database to ensure consistency. Each participant who chose the online survey reviewed a digital informed consent form detailing the study's purpose, procedures, confidentiality, and the right to withdraw at any time. Only participants who provided electronic consent (“I agree to participate”) were eligible to proceed with the survey. For participants who chose the paper-based version of the survey, a printed informed consent form was provided, outlining the study objectives, procedures, potential risks and benefits, confidentiality measures, and the voluntary nature of participation. Only women who signed the written informed consent form were included in the study and permitted to complete the paper questionnaire.

After delivery, relevant obstetric and neonatal data were obtained from the Damumed electronic medical database and medical charts. These records included demographic characteristics, maternal medical history, pregnancy complications, gestational age at delivery, birth outcomes, and postpartum health status. Data from the online questionnaire and medical records were linked and cross-validated using anonymized identifiers to ensure data accuracy, consistency, and participant confidentiality.

2.3.3 Diagnostic criteria

Births that occurred prior to the 37th week of gestation were classified as PTB. Subgroups of preterm birth classified according to gestational age, as extremely preterm (EPTB) with less than 28 weeks gestation, very preterm (VPTB) with 28 to less than 32 weeks gestation, moderate to late preterm (MLPTB) with 32 to less than 37 weeks gestation, recognizing that the timing of a preterm birth significantly affects both risks and outcomes for the infant [6,p. 3].

2.3.4 Bias validation and quality control

To ensure the reliability and validity of the findings, several bias-mitigation and data-validation strategies were implemented. Selection bias was reduced by recruiting participants from three regional centers representing different socioeconomic backgrounds. Information bias was controlled by using standardized, interviewer-administered questionnaires and by cross-checking demographic and clinical data against the Damumed database. Recall bias was minimized by collecting questionnaire data prospectively during antenatal visits. Data quality was ensured through double-entry, random record verification, and consensus-based resolution of discrepancies. Confounding factors such as maternal age, parity, education, smoking, and socioeconomic status were recorded and adjusted for in multivariate analyses.

2.3.5 Variables included in the analysis

Variables were selected based on biological plausibility, evidence from the literature, and data availability from the Damumed system, medical charts, and the online questionnaire. They were grouped into the following categories:

Dependent Variable:

Preterm birth (PTB), Extremely preterm, Very preterm, Moderate to late preterm.

Independent Variables:

1. Maternal demographic and socioeconomic factors: Age (years), marital status, education level, household income level, employment status and workload, housing stability (ownership, crowding, or temporary housing), health insurance coverage, access, and place of healthcare.

2. Maternal and paternal general health status: Self-reported general health of mother and father (good/fair/poor), presence of chronic conditions (e.g., hypertension, diabetes), maternal body mass index (BMI) early pregnancy, Pre-existing medical conditions (e.g., thyroid disease, anemia)

3. Reproductive and clinical factors: Age at first pregnancy and history of teenage pregnancy (<20 years), parity and gravidity, previous miscarriage or preterm birth, pregnancy complications (e.g., gestational diabetes, hypertensive disorders, vaginal bleeding, urinary tract infections).

4. Oral health–related variables: Self-reported oral symptoms include bleeding gums, tooth pain, tooth mobility, and bad breath

5. Oral healthcare utilization: frequency of dental visits

## 2.4 Research Methods of the Case-Control Study

2.4.1 Study groups

Cases and controls were selected from the previously established pregnancy cohort to evaluate the independent and combined effects of oral diseases and maternal risk factors on the likelihood of spontaneous preterm birth (PTB). This was achieved by comparing women with spontaneous preterm birth to those with term birth.

The minimum sample size for the study is set a ensure 80% statistical power and an alpha level of 0.05. With an odds ratio of 2.0, the minimum sample size would be around 58 cases (preterm birth group) and 116 controls (non-preterm birth group).

Inclusion criteria: women with singleton pregnancy, vaginal delivery, live birth, and signed informed consent for further investigation.

Exclusion criteria: multiple pregnancies, with concomitant pregnancy complications, stillbirth, pregnancy-induced hypertension, gestational diabetes, induced labor, preterm premature rupture of membranes, and caesarean section were excluded from the study.

2.4.2 Oral health examination

The oral health condition was assessed by a dentist who measured periodontal and dental conditions using disposable dental mirrors and a periodontal probe recommended by the WHO, 48-72 hours after delivery.

Dental condition was evaluated by measuring DMFT index (decayed, missing, filled teeth) and their components (D,M,F) were discriminated, which reflects the cumulative lifetime dental caries experience per participant.

The prevalence and severity of periodontal diseases were assessed using the following parameters: bleeding on probing (BOP), probing depth (PD), and clinical attachment loss (CAL).

Salivary sample collection was performed as follows: 1 mL of unstimulated saliva was collected immediately after the periodontal examination and placed in a refrigerator at −80 °C for further study. The procedure was developed and registered under Certificate No. 30427 on November 18, 2022, titled “Procedure for Screening Periodontium and Collecting Saliva for Molecular Biological Analysis to Study Indicators of Preterm Birth in the Second Trimester of Pregnancy.”

2.4.3 Diagnostic criteria

1)DMFT index:

D (Decayed): A tooth with visible caries characterized by cavitation, softened enamel or dentin, or a detectable softened wall or floor on gentle probing. Non-cavitated white-spot lesions were not recorded as decayed.

M (Missing): A tooth extracted or lost due to caries, as determined by the participant’s self-report or clinical judgment when other causes (e.g., trauma, orthodontic extraction) were excluded.

F (Filled): A tooth with one or more permanent restorations placed due to caries, without evidence of recurrent carious lesions.

The individual DMFT score was calculated as: DMFT = D + M + F

2)The Periodontal Screening and Recording (PSR) system developed by the American Dental Association (ADA) and the American Academy of Periodontology (AAP) [383].

3)The severity and stage of periodontitis were classified according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [384]. In this study, staging was determined based on clinical attachment loss (CAL), probing depth (PD), and tooth loss attributable to periodontitis, while radiographic bone loss was not assessed. The classification system defines stages I–IV to describe the severity and extent of periodontal destruction, as well as the complexity of management. This clinical application of the World Workshop criteria enables standardized diagnosis and comparison, even in the absence of radiographic data.

The staging component of the 2017 World Workshop classification reflects the severity, extent, and complexity of periodontitis. It provides a framework to describe the current level of tissue destruction and the potential difficulty of case management. Staging is primarily determined by clinical attachment loss (CAL), the extent and pattern of bone loss, tooth loss due to periodontitis, and the complexity of required treatment.

Stage I (Initial Periodontitis): Characterized by mild loss of periodontal support. Clinical attachment loss is 1–2 mm, probing depth usually ≤4 mm, and mostly horizontal bone loss. There is no tooth loss due to periodontitis.

Stage II (Moderate Periodontitis): Represents established periodontitis with 3–4 mm of attachment loss, probing depth ≤5 mm, and mostly horizontal bone loss. No tooth loss due to periodontitis.

Stage III (Severe Periodontitis with Potential for Additional Tooth Loss): Involves ≥5 mm of attachment loss and probing depth ≥6 mm. There may be vertical bone loss ≥3 mm, furcation involvement (Class II or III), and up to four teeth lost due to periodontitis. Complex treatment is often required.

Stage IV (Advanced Periodontitis with Potential for Loss of the Dentition): Indicates extensive destruction with potential impairment of mastication and oral function. There is ≥5 mm of attachment loss, deep probing depths, and five or more teeth lost due to periodontitis. The disease is associated with secondary occlusal trauma, tooth mobility, or severe bite collapse.

Each stage can be further described as localized (≤30% of teeth involved) or generalized (>30% of teeth involved), or as a molar/incisor pattern if limited to those areas.

2.4.4 Bias validation and quality control

To minimize potential sources of bias and ensure data quality, several control measures were implemented throughout the study.

(1) All pregnant women attending antenatal care during the recruitment period in the Atyrau, Aktobe, and Kyzylorda regions were invited to participate regardless of

their socioeconomic background or oral health status. This universal recruitment method reduced selection bias. The final inclusion was based on verification of postpartum medical records to ensure accurate classification of pregnancy outcomes.

(2) The structured questionnaire was pretested in a pilot survey and administered in both online and paper formats to enhance accessibility and comprehension. Data entry was double-checked to identify and correct inconsistencies or missing responses. Duplicate or incomplete questionnaires were excluded from the analysis.

(3) All clinical dental examinations were performed by a single calibrated dentist to ensure diagnostic consistency. Intra-examiner reliability was confirmed by re-examining 10% of participants after a 7-day interval, with consistent findings across repeated assessments.

(4) Standardized diagnostic criteria were applied for DMFT and periodontal assessments based on WHO and AAP/ADA recommendations. Disposable dental instruments were used for each participant, and periodontal probing was performed under consistent lighting and infection-control conditions.

(5) Completed questionnaires and clinical forms were verified for completeness before inclusion. All data were anonymized, coded, and entered into a password-protected database with restricted access. Periodic data audits were conducted to ensure accuracy and reliability.

2.4.5 Variables included in the analysis

(a) Sociodemographic variables: Maternal age (years), educational level (secondary, college, university), employment status (employed/unemployed), marital status (married/single), monthly household income (categorized according to national thresholds), housing stability (own/rented/temporary).

(b) Maternal health and behavioral factors: Parity and gravidity, history of preterm birth or miscarriage, body mass index (BMI, kg/m²) early pregnancy, presence of chronic diseases (e.g., hypertension, diabetes), ntenatal care utilization (number and timing of visits), smoking or alcohol use during pregnancy, oral hygiene practices (tooth brushing frequency, dental visits).

(c) Oral health indicators: DMFT index (Decayed, Missing, Filled Teeth), bleeding on probing (BOP, %), probing depth (PD, mm), clinical attachment loss (CAL, mm), periodontitis stage (I–IV), periodontal Screening and Recording (PSR) score

(d) Pregnancy outcome: Spontaneous preterm birth and term birth.

## 2.5 Methods of Fusobacterium nucleatum Detection

2.5.1 The study population

The study sample for this molecular component was drawn from the same case and control groups described in Section 2.2.3.1. Specifically, pregnant women from the cohort who delivered at perinatal centers in the Atyrau, Aktobe, and Kyzylorda regions were included. Women with spontaneous preterm birth (<37 weeks) comprised the case group, while those with term birth (≥37 weeks) served as controls.

2.5.2 Sample collection procedure

Placental tissue was obtained only after the umbilical cord was severed by an obstetrician–gynecologist. Within 24 hours postpartum, a paracentral placental biopsy (approximately 1 cm × 1 cm × 3 cm), including fetal membranes and decidua, was excised from separate areas using sterile instruments. Each specimen was placed into a sterile container and stored at −80 °C until analysis [236,p. 556].

In addition, salivary samples were collected during the oral health examination (as described in Section 2.2.3.4). Each participant provided approximately 1 mL of unstimulated whole saliva obtained by passive drooling into sterile Eppendorf tubes. Samples were immediately placed on ice and transported to the laboratory, where they were stored at −80 °C until DNA extraction and quantification of Fusobacterium nucleatum [236,p. 556].

2.5.3 DNA Extraction from saliva and placental tissue

Genomic DNA was extracted from saliva using the *QIAamp DNA Blood Kit* (Cat. No. 51104, Qiagen, Germany) and from placental tissue using the *AllPrep DNA/RNA/miRNA Universal Kit* (Cat. No. 80224, Qiagen, Germany), following the manufacturer's protocols [385,386]. Prior to DNA extraction, placental samples were homogenized using the MT-13K-L Mini Handheld Homogenizer (Hangzhou Miu Instruments) in lysis buffer containing guanidine isothiocyanate to ensure efficient cell disruption, protein denaturation, and DNase inactivation. The purity and concentration of extracted genomic DNA were evaluated using the BioTek Synergy LX Multi-Mode Microplate Reader (Agilent, USA) [387].

2.5.4 Quantification of Fusobacterium nucleatum by TaqMan qPCR

Quantitative detection of *Fusobacterium nucleatum* DNA was performed using a custom TaqMan-based real-time quantitative PCR assay targeting the *nusG* gene [386,p. 417]. The human SLCO2A1 gene was used as the internal reference for normalization. The following primers and probes were designed:

F.nucleatum:

Forward primer: 5′-TGG TGT CATTCTTCCAAAAATATCA-3′, Reverse primer: 5′-AGA TCA AGA AGG ACA AGT TGC TGA A-3′, Probe (FAM-labeled): 5′-ACT TTA ACT CTA CCA TGT TCA-3′.

SLCO2A1 (endogenous control):

Forward primer: 5′-ATC CCC AAA GCA CCT GGT TT-3′, Reverse primer: 5′-AGA GGC CAA GAT AGT CCT GGT AA-3′, Probe (VIC-labeled): 5′-CCA TCC ATG TCC TCA TCT C-3′.

Each qPCR reaction was conducted in a 384-well optical PCR plate using the LightCycler 480 Instrument II (Roche Diagnostics, Switzerland). The PCR reaction mixture included template DNA, custom primers and probes, and TaqMan Universal PCR Master Mix. The amplification conditions were: initial denaturation at 95 °C for 10 min, followed by 40 cycles of Denaturation at 95 °C for 15 sec and Annealing/extension at 60 °C for 60 sec [385,p. 28].

To ensure the validity and reliability of the qPCR results, standard controls were included in each run. Negative controls (no-template controls) containing nuclease-free water instead of DNA template were used to monitor potential contamination or non-specific amplification. Positive controls consisting of genomic DNA from a verified *F. nucleatum* reference strain (ATCC 25586) were included to confirm assay sensitivity and efficiency. Each sample was analyzed in triplicate to ensure reproducibility [387,p. 611].

The threshold cycle (Ct) values were automatically determined by the LightCycler software, and *F. nucleatum* DNA levels were normalized to *SLCO2A1* expression. Internal assay performance was evaluated by assessing amplification efficiency (90–110%), linear dynamic range ($R^2 \geq 0.98$), and intra-assay coefficient of variation (< 5%). Data were expressed as relative abundance of *F. nucleatum* using the comparative $\Delta$Ct method [388].

### 2.6 Ethical Considerations

Ethical approval was obtained from the Al-Farabi Kazakh National University Ethical Committee (IRB-A308). The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, and permission was obtained from the hospital authorities to access the patients' medical records. The author who analyzed the data did not have access to personal data.

### 2.7 Statistical analysis

To ensure analytical robustness, the study combined classical statistical methods with ML-based explainable modeling. Traditional biostatistical tests were employed to identify significant maternal, clinical, and oral health determinants of PTB. At the same time, ML models were applied to explore nonlinear relationships and predictive patterns among multidimensional variables. This complementary approach enhanced both interpretability and predictive validity, linking statistically confirmed associations to model-derived feature importance.

#### 2.7.1 Traditional statistical analysis

All data were entered into SPSS. Descriptive statistics were used to summarize maternal sociodemographic characteristics, clinical variables, and oral health parameters. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on the distribution of the data, whereas categorical variables were reported as frequencies and percentages.

Comparisons between the preterm and term birth groups were performed as follows: the chi-square ($\chi^2$) test was applied to assess associations between categorical variables. Mann–Whitney U test was used for non-normally distributed continuous variables. Pearson's correlation coefficient (r) was used to evaluate linear relationships between quantitative variables. Variables that demonstrated significance at $p < 0.1$ in univariate analyses were included in a multivariable logistic regression model to identify independent predictors of spontaneous preterm birth. Both crude and adjusted

odds ratios (OR) with 95% confidence intervals (CI) were reported. Statistical significance was considered at $p < 0.05$.

Mantel test: To explore multivariate interrelationships between maternal, clinical, and oral health parameters, a Mantel test–based correlation network was constructed. The Mantel test evaluates the correlation between distance matrices, allowing assessment of the overall association structure among variables. Pairwise Pearson's correlation coefficients (r) quantified the linear relationships between individual variables, while Mantel's r captured global associations across variable clusters (e.g., oral health indicators, pregnancy outcomes, and sociodemographic factors). In the correlation matrix, Pearson's r values are represented by colored squares (ranging from -1.0 to +1.0), where blue tones indicate positive correlations and red tones negative correlations. Mantel's r values are shown as connecting lines between nodes, with line thickness reflecting the strength of the relationship (< 0.2 = weak, 0.2–0.4 = moderate, > 0.4= strong). Statistical significance was denoted by p-value ranges (< 0.01, 0.01–0.05, > 0.05). This analysis demonstrated a network of interrelated factors linking DMFT, periodontitis, and spontaneous preterm birth, with notable correlations between maternal socioeconomic characteristics, oral hygiene behaviors, and clinical indicators of periodontal inflammation (bleeding on probing, PSR, and BOP).

2.7.2 Machine Learning and Explainable AI Analysis

To assess the relative contributions of clinical, demographic, and oral health parameters to the risk of spontaneous preterm birth (PTB), supervised machine learning (ML) models were applied to a nested case–control dataset comprising 90 PTB cases and 180 term controls. The dataset was randomly partitioned into training (80%) and testing (20%) subsets using stratified sampling to maintain class balance. Missing data were handled using the MissForest imputation algorithm, which applies random forest–based iterative estimation to preserve nonlinear relationships and complex feature interactions.

Six supervised ML algorithms were trained and compared: logistic regression (LR), random forest (RF), gradient boosting machine (GBM), extreme gradient boosting (XGBoost), support vector machine (SVM), and multilayer perceptron (MLP). Hyperparameters for each model were optimized via grid search with 10-fold cross-validation to prevent overfitting and ensure generalizability. Based on cross-validation performance, a stacking ensemble model integrating tree-based and linear classifiers was selected as the final predictive framework for PTB classification.

Model performance was evaluated on the independent test subset using area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity. Repeated 10-fold cross-validation was applied to confirm the robustness and stability of model predictions.

To improve interpretability and link model predictions with clinical relevance, explainable artificial intelligence (AI) methods were incorporated. SHAP (SHAPley Additive exPlanations) was employed to quantify the individual and overall contributions of each feature to PTB prediction. SHAP summary plots were generated

to rank variables by their mean absolute SHAP values, while waterfall and force plots visualized the effects of features at the patient level. For comparative validation, Local Interpretable Model-agnostic Explanations (LIME) were also applied, confirming consistency in the direction and magnitude of key predictor influences.

This integrated ML–XAI approach provided a complementary perspective to traditional regression analysis, enabling both predictive modeling and mechanistic interpretation of how maternal, behavioral, and oral health factors interact to contribute to the risk of spontaneous preterm birth.

# 3 RESULTS OF THE STUDY

## 3.1 Result of systematic review and Meta-analysis

3.1.1 The main result of the analysis

The search strategy resulted in 3769 potentially relevant citations. Of the 2307 studies initially searched, 2307 were excluded from further analysis after screening the titles and abstracts. Key data were extracted from the included studies, including the authors' names and publication years, study designs, numbers of participants, and definitions of oral diseases, particularly periodontitis, dental caries, and periapical infection. The characteristics of the selected studies are detailed in Appendix A, providing a comprehensive overview of the study populations and methodologies. To assess the quality and reliability of the included studies, the Newcastle–Ottawa Scale (NOS) was used, and the results are summarized in Appendix A. This systematic and thorough approach ensured that the findings are robust and reliable, providing valuable insights into the potential relationship between oral health status and preterm birth.

3.1.2 Periodontitis and Preterm Birth

After screening titles and abstracts, we reviewed 67 full-text articles and included 29 studies with comparable outcomes. The twenty nine study involve the 1343 pregnant participants assessed the oral infection on preterm birth in this study, compared with pregnant women without apical periodontitis, the pregnant women with apical periodontitis regardless of the diagnostic criteria and other factors were at higher risk of experience preterm birth [OR =1.81, CI = 1.60 to 2.03; p <0.001; $I^2$ = 95%] (figure 3).

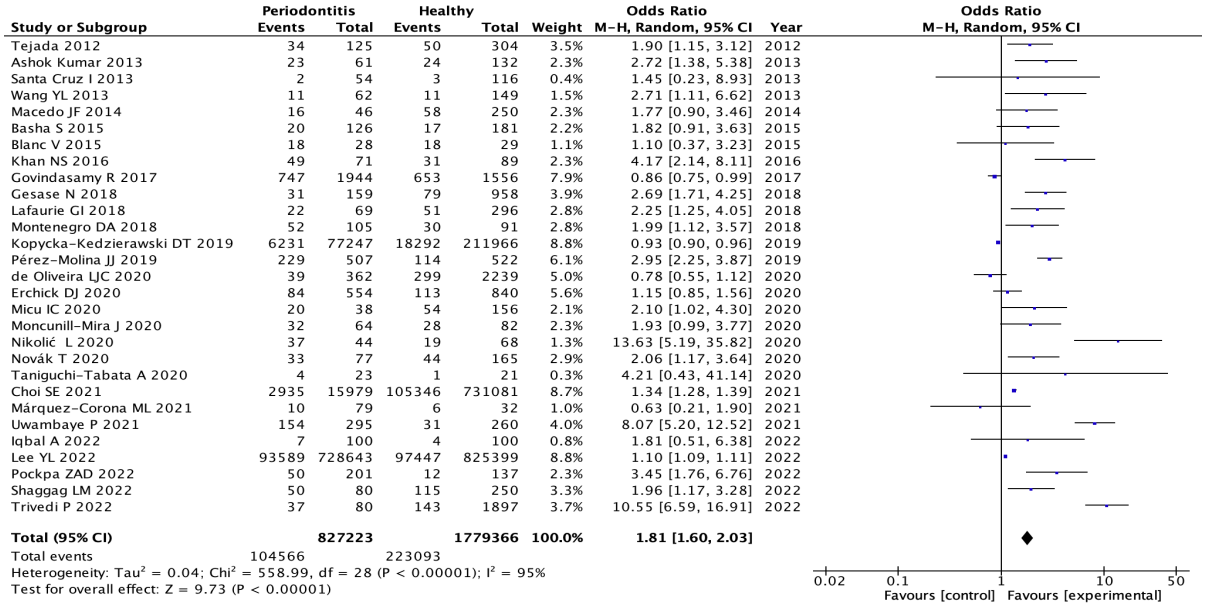


Figure 3 – Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the periodontitis and preterm birth

3.1.3 Dental caries  and Preterm birth

After screening titles and abstracts, we reviewed 67 full-text articles and included 11 studies with comparable outcomes. A meta-analysis of five studies assessed the relationship between dental caries, measured by DMFT (Decayed, Missing, and Filled Teeth) scores, and preterm birth. The pooled analysis showed that pregnant women who experienced preterm birth had significantly higher DMFT scores compared to those who delivered at term, with a summary mean difference of 1.56 (95% CI: 0.28 to 3.41). This indicates that poorer dental health was more prevalent among the preterm birth group. However, heterogeneity was high ($I^2$ = 92%), indicating substantial variability across studies, likely attributable to differences in study populations, methodologies, or diagnostic criteria. Despite this, the overall trend supports a potential association between increased dental caries burden and the risk of preterm delivery. (figure 4).

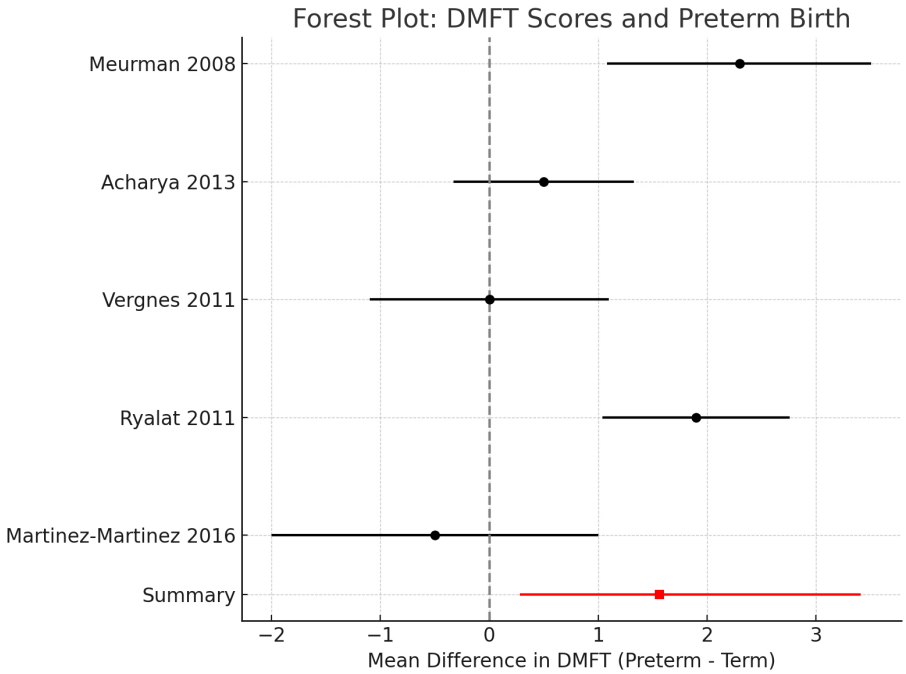


Figure 4 – Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the DMFT and preterm birth

3.1.4 Periapical infection and Preterm birth

After screening the titles and abstracts, three study were included in analysis. The included studies were published between 2015 and 2017 and reported a total of 1987 participants, with an approximate age range of 15 to 40 years. The overall quality of the evidence was ‘Fair’ for two out of five included studies, while one study was categorized as ‘Good’.e oral infection on preterm birth in this study, compared with pregnant women without periodical infection, the pregnant women with apical periodontitis regardless of the diagnostic criteria and other factors were at similar risk of experience preterm birth [OR =2.14, CI=1.43-3.20; $p < 0.05$; $I^2$ = 18.6%] (figure 5).

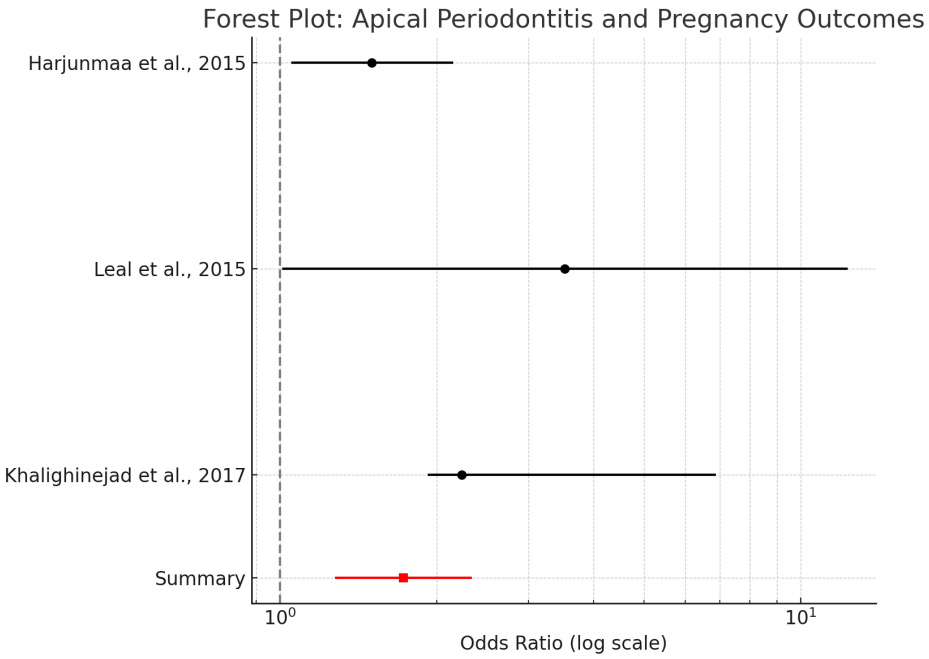


Figure 5 – Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the Apical infection and preterm birth

3.1.5 Discussion of the results

This systematic review and meta-analysis assessed three major oral health conditions—periodontitis, dental caries, and periapical infection—and their associations with preterm birth (PTB). The findings of this review contribute to an expanding body of evidence suggesting that oral infections, particularly periodontal disease, may play a significant role in adverse pregnancy outcomes.

Our analysis, which included 29 studies and 1343 pregnant participants, demonstrated a significant association between periodontitis and preterm birth (OR = 1.81, 95% CI 1.60–2.03; $p < 0.001$). This finding is consistent with multiple international meta-analyses. A systematic review by Xiong et al. reported that women with periodontitis had nearly twice the risk of PTB compared with periodontally healthy women [389]. In contrast, Vergnes and Sixou reported a pooled OR of 1.82—almost identical to the estimate from our analysis [390]. Similarly, Chambrone et al. [391] reported that moderate-to-severe periodontitis increases the risk of PTB by 1.5–2.2 times across large observational cohorts, and Corbella et al. [392] provided further support with comparable effect sizes.

Several mechanistic studies support the biological plausibility of this association. Periodontitis is characterized by chronic inflammation and dysbiosis, with pathogens such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Tannerella forsythia* capable of translocating hematogenously to the placental–fetal unit. These microorganisms and their virulence factors induce systemic inflammatory mediators (IL-6, TNF-α, prostaglandins), which are known triggers of uterine contractions and cervical ripening. Studies using placental tissue analysis and cord blood cultures have

repeatedly demonstrated the presence of oral bacteria in the intrauterine environment, supporting a mechanistic link between periodontal inflammation and preterm labor [270,p. 32].

Although the relationship between periodontitis and PTB is well documented, heterogeneity across studies remains high ($I^2$ = 95%). This is consistent with earlier systematic reviews and reflects variability in diagnostic criteria, periodontal measurement techniques, gestational age definitions, and adjustment for confounding factors, including smoking, obesity, socioeconomic status, and access to antenatal dental care. Nevertheless, the direction of effect across most studies remains positive and statistically significant, reinforcing periodontitis as a clinically meaningful modifiable risk factor.

The association between dental caries and PTB was less consistent. Our analysis of five studies using DMFT scores indicated higher caries experience in women with preterm birth (mean difference = 1.56), but high heterogeneity ($I^2$ = 92%) precludes firm conclusions. International literature supports this ambiguity. Two large Brazilian cohort studies and several European investigations found no clear association between dental caries and PTB after adjustment for socioeconomic and dietary factors [243,p. 305]. However, studies from India and Southeast Asia reported higher risks in women with untreated caries [248,p. 1125], suggesting that population differences, nutritional patterns, and oral hygiene practices may influence outcomes.

It is notable that dental caries, unlike periodontitis, is often not associated with significant systemic inflammation unless complicated by pulpitis or periapical spread. The absence of robust biological pathways, combined with methodological heterogeneity, likely accounts for the inconsistent evidence. Thus, although our findings suggest a trend toward a higher caries burden in the PTB group, current evidence does not support dental caries as a reliable predictor of preterm birth.

Evidence relating periapical infections to PTB remains limited. Our pooled analysis of three studies (n =1,987) found a significant association (OR = 2.14, 95% CI 1.43–3.20) with low heterogeneity ($I^2$ = 18.6%), indicating consistency across the available literature. This result aligns with a growing number of case–control studies from Japan, Brazil, and Turkey suggesting that untreated periapical lesions—particularly chronic apical periodontitis-may contribute to systemic inflammatory burden [245,p. 1428].

Periapical infections share biological pathways with periodontal disease, including bacterial translocation, elevated systemic inflammatory biomarkers, and immune dysregulation. However, evidence is still sparse, with few high-quality prospective studies available. International reviews specifically examining dental pulp disease as a risk factor remain scarce, making our findings particularly valuable. As such, the association between periapical infection and PTB should be interpreted cautiously but warrants further controlled investigation. Across all three conditions, our findings align closely with those reported in global systematic reviews. Periodontitis consistently demonstrates the strongest and most reproducible association with PTB across diverse populations, including large studies in the United States, Brazil, China, India, and South Africa [238,p. 324]. Studies from Scandinavian birth

registries and Japanese prospective cohorts similarly report significant associations between maternal periodontal status and PTB or low birth weight [247,p. 1567]. By contrast, the role of dental caries and periapical infection remains less clearly defined in global literature. Some studies identify these oral diseases as indirect indicators of poor oral hygiene, low socioeconomic status, or limited access to care—factors that independently contribute to PTB risk [255,p. 305]. The limited number of high-quality studies on periapical disease globally is a major gap highlighted by both our findings and international evidence. Notably, very few studies originate from Central Asia, indicating a significant research gap and underscoring the relevance of your dissertation in addressing oral health and pregnancy outcomes in Kazakhstan [363,p. 45]. This review emphasizes the importance of distinguishing between types of oral infections when assessing their impact on pregnancy outcomes. Periodontitis appears to be a true biological risk factor for PTB, supported by robust epidemiological and mechanistic evidence. Dental caries and periapical infections may contribute indirectly through systemic inflammation or may serve as markers of broader health disparities; however, current data are insufficient to confirm causality.

### 3.2 Result of the cohort study

3.2.1 Sample characteristics

A total of 2235 pregnant women were successfully followed up [27,p. 769]. 80 (12.5%) cases of singleton preterm birth (PTB) were reported. Of these PTB cases, 39 (14%) were classified as EPTB, 41 (15%) as VPTB, and 200 (71%) as MLPTB, representing 1.7%, 1.8%, and 8.9% of the total sample, respectively, as shown in figure 6.

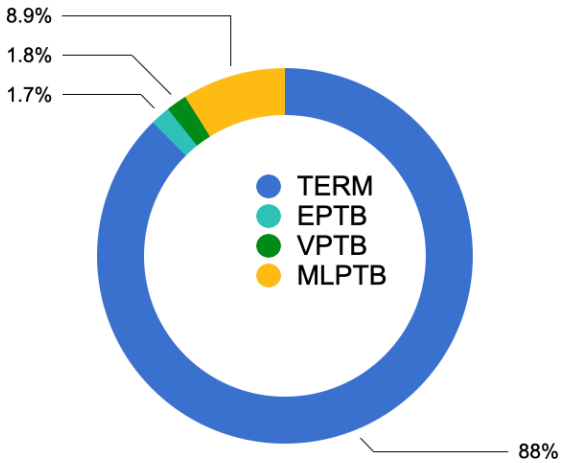


Figure 6 – Distribution of PTB by gestational age category among the Study groups

The mean age of the sample was 29.5 (5.9) years, with no difference between term and preterm mothers (p = 0.66). Regarding the overall sample characteristics, 98%

were ethnic Kazakhs, 88% had a higher education (more than 12 years), and 63% were employed. None reported smoking and consuming alcohol during pregnancy—the details of the sample are represented in the following (figure 7).

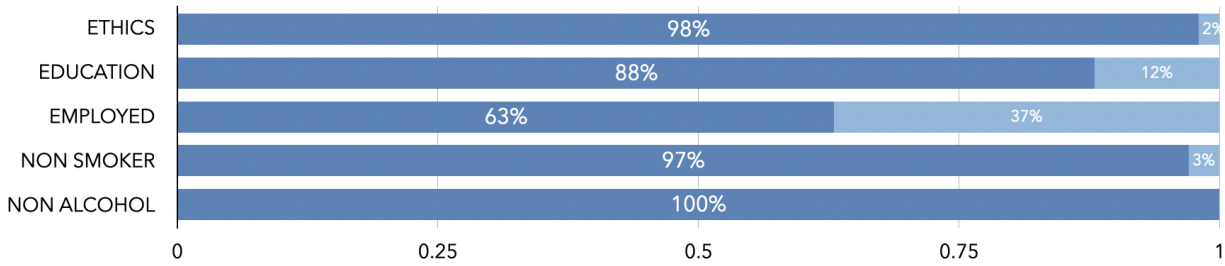


Figure 7 – Distribution of Sociodemographic and Lifestyle Characteristics Among the Study Population

3.2.2 Factors and preterm birth

The maternal demographic variables include maternal age, pre-pregnancy body weight, height, BMI, gravida status, and age at first pregnancy.

Maternal Age: The majority of women in both the term and preterm groups were aged 25-29 years, accounting for 30.3% and 25.4%, respectively. Although the proportion of younger mothers (<20 years) was higher among preterm births (6.1%) compared with term births (4.7%), the difference was not statistically significant. Similarly, maternal age did not differ significantly across EPTB, VPTB, and MLPTB categories ($p$ = 0.8, 0.5, and 0.7, respectively).

Table 1 – Association between maternal age and PTB categories

| Variables | Term (n=1955) | PTB (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Age, years | | | | | | | | | |
| <20 | 91 (4.7) | 17 (6.1) | 0.2 | 3(7.7) | 0.3 | 2(4.9) | 0.5 | 12(6) | 0.7 |
| 20-24 | 475 (24.3) | 73 (26.1) | | 8(20.5) | | 13(32) | | 52(26) | |
| 25–29 | 593(30.3) | 71(25.4) | | 7 (17.9) | | 8 (20) | | 56(28) | |
| 30-34 | 454(23.2) | 59 (21.1) | | 11 (28.2) | | 8(19.5) | | 40(20) | |
| >35 | 342 (17.5) | 60(21.4) | | 10(25.6) | | 10(24.4) | | 40 (20.0) | |

Pre-pregnancy Weight: A statistically significant association was observed between pre-pregnancy weight and preterm birth ($p$ = 0.002). Among women with preterm births, 43.9% were classified as obese or overweight, 45.4% had normal weight, and 10.7% were underweight. In the EPTB group, more than half of the women

(53.8%) had a normal weight, while 41% were obese or overweight. The VPTB subgroup showed a similar distribution, with 53.7% of women in the normal weight category and 34.1% obese or overweight ($p$ = 0.1). In contrast, the MLPTB group demonstrated a significant association ($p$ = 0.002), where 46.5% of women were obese or overweight and 11.5% were underweight. These findings suggest that both extremes of maternal weight may influence the risk of preterm birth.

Table 2 – Association between BMI and PTB categories

| Variables | Term (n=1955) | PTB (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Obese/overweight | 898 (45.9) | 123 (43.9) | 0.002 | 16 (41) | 0.8 | 14 (34.1) | 0.1 | 93 (46.5) | 0.002 |
| Normal weight | 952 (48.7) | 127 (45.4) | | 21 (53.8) | | 22 (53.7) | | 84 (42.0) | |
| Underweight | 105(5.4) | 30 (10.7) | | 2 (5.1) | | 5 (12.2) | | 23 (11.5) | |

Age at First Childbirth: A highly significant relationship was identified between maternal age at first childbirth and preterm birth ($p < 0.001$). Most term births occurred among women aged 20–25 years at first childbirth (65.0%), while a greater proportion of preterm births occurred among those younger than 20 years (18.2%). In the EPTB and VPTB groups, 59.0% and 63.4% of mothers, respectively, gave birth to their first child at 20–25 years ($p < 0.05$). The MLPTB group showed similar trends, with the highest proportion (51.0%) also in the 20–25-year age group. Interestingly, women aged over 30 years at first childbirth accounted for 12.0% of MLPTB cases, suggesting an elevated risk for late maternal age as well.

Table 3 – Association between age at first pregnancy and PTB categories

| Variables | Term (n=1955) | PTB (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| <20 years | 310 (15.9) | 51 (18.2) | 0.001 | 10 (25.6) | 0.20 | 2 (4.9) | 0.02 | 39 (19.5) | 0.001 |
| 20–25 years | 1270 (65.0) | 151 (53.9) | | 23 (59.0) | | 26 (63.4) | | 102(51.0) | |
| 26-30 years | 279 (14.3) | 48 (17.1) | | 6 (15.4) | | 7 (17.1) | | 35 (17.5) | |
| >30 years | 96 (4.9) | 30 (10.7) | | 0 | | 6(14.6) | | 24(12.0) | |

3.2.3 Obstetrical history and preterm birth

The maternal complications during pregnancy and obstetrical history include gestational diabetes, preeclampsia, history of miscarriage, abortion, and preterm birth, and gravida. A history of miscarriage was reported in 21.8% of women with preterm births compared with 19.4% among those with term births. However, this difference

was not statistically significant ($p$ = 0.35). Similarly, no significant differences were observed across EPTB ($p$ = 0.35), VPTB ($p$ = 0.22), or MLPTB ($p$ = 0.22) subgroups. The proportion of women with a history of abortion was nearly identical between preterm (9.6%) and term (9.4%) groups, indicating no significant association ($p$ = 0.90). Subgroup analyses also revealed no significant differences for EPTB ($p$ = 0.48), VPTB ($p$ = 0.64), or MLPTB ($p$ = 0.98). Therefore, a prior abortion history was not associated with increased preterm birth risk. The association between miscarriage and abortion is shown in Table 4.

Table 4 – Association between miscarriage, abortion and PTB categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Miscarage | | | | | | | | | |
| Yes | 379 (19.4) | 61(21.8) | 0.35 | 10 (25.6) | 0.35 | 5 (12.2) | 0.22 | 46 (23.0) | 0.22 |
| No | 1576(80.6) | 219 (78.2) | | 29 (74.4) | | 36 (87.8) | | 1564(77.0) | |
| Abortion | | | | | | | | | |
| Yes | 184 (9.4) | 27 (9.6) | 0.90 | 5 (12.8) | 0.48 | 3 (7.3) | 0.64 | 19 (9.5) | 0.98 |
| No | 1771 (90.6) | 253 (90.4) | | 34 (87.2) | | 38 (92.7) | | 181 (90.5) | |

Gestational Diabetes Mellitus (GDM): The prevalence of gestational diabetes was low across all groups, with 3.9% among preterm and 2.5% among term deliveries. The overall difference was not statistically significant ($p$= 0.15). However, subgroup analysis showed a significant association with VPTB ($p$= 0.004), with 9.8% of women having GDM compared with 2.5% in term births. No significant association was observed for EPTB ($p$ = 0.30) or MLPTB ($p$ = 0.43).

Preeclampsia: Preeclampsia was identified in 6.4% of preterm births and 8.3% of term births, indicating no significant difference ($p$ = 0.29). Similarly, no significant associations were observed across the preterm subgroups: EPTB ($p$ = 0.18), VPTB ($p$ = 0.18), and MLPTB ($p$ = 0.98). Thus, in this study population, preeclampsia did not appear to influence the risk of preterm birth significantly.The association between GDM and preeclampsia is shown in Table 5.

Table 5 – Association between GDM, preeclampsia and PTB categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Gestational diabet | | | | | | | | | |
| Yes | 48 (2.5) | 11 (3.9) | 0.15 | 0 | 0.30 | 4 (9.8) | 0.004 | 7 (3.5) | 0.43 |

Continuation of table 5

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| No | 1907 (97.5) | 269 (96.1) | | 39 (100) | | 37 (90.2) | | 193 (96.5) | |
| Preeclampsia | | | | | | | | | |
| Yes | 162 (8.3) | 18 (6.4) | 0.29 | 1 (2.6) | 0.20 | 1 (2.4) | 0.18 | 16 (8.0) | 0.98 |
| No | 1793 (91.7) | 262 (93.6) | | 38 (97.4) | | 40 (97.6) | | 184 (92.0) | |

A previous history of preterm birth was found to be strongly associated with subsequent preterm delivery. The association remained highly significant across all subgroups: EPTB: 43.6% with prior PTB ($p < 0.001$); VPTB: 36.6% with prior PTB ($p = 0.001$); MLPTB: 47.5% with prior PTB ($p < 0.001$).Primigravida women (first pregnancy) accounted for 21% of preterm births, compared with 16% of term births. Within subcategories, EPTB and MLPTB groups showed no significant differences ($p = 0.28$ and 0.18, respectively), whereas the VPTB group revealed a strong association ($p = 0.001$), with 63.4% of cases occurring among primigravida women.

Table 6 – Association between gravida,history of PTB and PTB categories

| Variables | Term (n=1955) | PTB (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Primigravida | 312 (16) | 59 (21) | 0.03 | 4 (10.3) | 0.28 | 26 (63.4) | 0.001 | 40 (20.0) | 0.18 |
| Multigravida | 1643(84) | 221(79) | | 35 (89.7) | | 15 (36.6) | | 160 (80.0) | |
| History of preterm | | | | | | | | | |
| Yes | 263 (13.5) | 127 (45.4) | 0.001 | 17 (43.6) | 0.001 | 15 (36.6) | 0.001 | 95 (47.5) | 0.001 |
| No | 1692 (86.5) | 153 (54.6) | | 22 (56.4) | | 26 (63.4) | | 105 (52.5) | |

3.2.4 Socio-economic status and preterm birth

Marital Status: The majority of participants in both groups were married. Divorced, widowed, or separated women represented 3.0% of term and 4.3% of preterm pregnancies, showing no statistically significant difference ($p = 0.26$). However, within subgroups, marital status was significantly associated with extreme preterm birth (EPTB), where divorced or widowed mothers had a higher proportion of EPTB ($p < 0.001$). No significant associations were found for very preterm or moderate-to-late preterm births ($p > 0.05$). Housing conditions demonstrated a significant association with preterm birth overall ($p = 0.02$). The majority of term deliveries were among women living in rented or mortgaged housing (69.6%), compared to 76.8% among preterm cases. Women who owned their homes had a lower

proportion of preterm births (14.6%) than those who did not (21.6%). Subgroup analysis howed no statistically significant relationship.

Table 7 – Association Between marital status, housing stability and PTB categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Marital status | | | | | | | | | |
| Marid | 1896 (97.0) | 268 (95.7) | 0.26 | 33 (84.6) | 0.001 | 41 (100) | 0.23 | 194 (97.0) | 0.81 |
| Divorced, widowed,separated | 59 (3.0) | 12 (4.3) | | 6 (15.4) | | 0 | | 6(3.0) | |
| Housing stability | | | | | | | | | |
| Homeless or housing with parents | 172 (8.8) | 24 (8.6) | 0.02 | 3 (7.7) | 0.66 | 2 (4.7) | 0.21 | 19 (9.5) | 0.11 |
| Owned | 422 (21.6) | 41 (14.6) | | 6 (15.4) | | 5 (11.6) | | 30 (15.0) | |
| Rent or loan | 1361 (69.6) | 215 (76.8) | | 30 (76.9) | | 34 (83.7) | | 151 (75.5) | |

Employment status was not associated with preterm birth (p = 0.89). Joblessness was reported in 9.6% of term and 10.7% of preterm participants, while housewives constituted approximately one-quarter of both groups (27.9% vs. 26.1%). Similarly, no significant differences were observed among preterm birth subtypes (p > 0.05). More than half of all respondents reported earning between two and five minimum wages (57.9% in both groups). Low-income families (≤2 minimum wages) accounted for 29.0% of term and 31.1% of preterm births, whereas higher-income households (≥6 minimum wages) accounted for approximately 13% of term and 11% of preterm births. No significant associations were observed across preterm subtypes (p = 0.44–0.51). Women with completed secondary or technical education accounted for 24.4% and 28.6%, respectively, whereas those with incomplete schooling accounted for approximately 12% in both groups. No significant variation was observed across preterm birth subtypes (p > 0.05).

Table 8 – Association Between Employment, income, education and PTB categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Employment | | | | | | | | | |
| Jobless | 187 (9.6) | 30 (10.7) | 0.89 | 0 | 0.05 | 8 (19.5) | 0.07 | 22 (11.4) | 0.74 |
| Housewife | 545 (27.9) | 73 (26.1) | | 17 (43.6) | | 6 (14.6) | | 50 (25.0) | |

Continuation of table 8

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Employee | 1140 (58.3) | 165 (58.9) | | 21 (53.8) | | 26 (63.4) | | 118 (58.4) | |
| Income | | | | | | | | | |
| ≤2 minimum wages | 567 (29.0) | 87 (31.1) | 0.57 | 15(38.5) | 0.44 | 15(36.6) | 0.48 | 57 (28.5) | 0.51 |
| 2–5 minimum wages | 1132 (57.9) | 162 (57.9) | | 20(51.3) | | 20(51.5) | | 122 (61.0) | |
| ≥6 minimum wages | 256 (13.1) | 31 (11.1) | | 4 (10.3) | | 6 (14.6) | | 21 (10.5) | |
| Education | | | | | | | | | |
| uncompleted school | 243(12.4) | 32 (11.4) | 0.32 | 8 (20.5) | 0.29 | 7 (17.1) | 0.64 | 17 (8.5) | 0.07 |
| completed school or technical College | 477(24.4) | 80 (28.6) | | 9(23.1) | | 10 (24.4) | | 61 (30.5) | |
| University or higher | 1235(63.2) | 168(60.0) | | 22 (56.4) | | 24 (58.5) | | 122 (61.0) | |

Main Breadwinner of the Family: In most families, the husband was the primary income provider (74.8% term and 70.4% preterm). A smaller proportion reported that the wife (12.5% vs. 14.6%) or both spouses (3.8% vs. 4.6%) were the breadwinners, with no statistically significant differences ($p = 0.34$). The pattern remained consistent across EPTB, VPTB, and MLPTB ($p > 0.05$). No significant relationship was found between the husband's working load and preterm birth ($p = 0.22$). Most husbands worked full-time or more (around 65%), while 11–14% were jobless. The distribution did not differ significantly between term and preterm births or among subtypes ($p > 0.20$).

Table 9 – Association Between family provider and PTB Categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Main breadwinner of family | | | | | | | | | |
| Husband | 1463 (74.8) | 197 (70.4) | 0.34 | 23 (59) | 0.16 | 28 (69.8) | 0.81 | 146 (73.0) | 0.92 |
| Wife | 245 (12.5) | 41 (14.6) | | 8 (19.5) | | 8 (18.6) | | 25 (12.5) | |
| Both husband and wife | 75 (3.8) | 13 (4.6) | | 3 (2.4) | | 1 (2.3) | | 9 (10.2) | |

Continuation of table 9

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Other member | 172 (8.8) | 29 (10.4) | | 5 (12.8) | | 4 (9.3) | | 20(10.0) | |
| Working load of husband | | | | | | | | | |
| Jobless | 217 (11.1) | 41 (14.6) | 0.22 | 5(12.8) | 0.93 | 7 (17.1) | 0.25 | 29 (14.5) | 0.23 |
| Part time | 467 (23.9) | 56 (20.0) | | 8 (20.5) | | 9 (21.9) | | 39 (19.5) | |
| Full time | 647 (33.1) | 90 (32.1) | | 12 (30.8) | | 17 (41.5) | | 61 (30.5) | |
| Full time plus part time | 624 (31.9) | 93 (33.2) | | 14(35.9) | | 8 (19.5) | | 71 (35.5) | |

Social Support from Government: Approximately one-fourth of participants reported receiving social support from the government (26.4% of term and 23.9% of preterm). The difference was not statistically significant (p = 0.38). Likewise, no significant differences were observed in EPTB, VPTB, or MLPTB categories (p > 0.05).

Principal Place of Health Care: Most women received antenatal and delivery care in government hospitals, whereas approximately one-third attended private clinics (30.8% vs. 32.9%). Only a small fraction used both sectors (3.6% vs. 5.0%). Although the overall association between place of healthcare and preterm birth was not significant (p = 0.39), a strong association was observed with very preterm birth (VPTB).

Table 10 – Association Between social support, health care facility and PTB Categories

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | ***P*** |
|---|---|---|---|---|---|---|---|---|---|
| Social support from government | | | | | | | | | |
| With | 516 (26.4) | 67 (23.9) | 0.38 | 11 (28.2) | 0.76 | 14 (34.1) | 0.24 | 42 (20.8) | **0.08** |
| Without | 1439 (73.6) | 213 (76.1) | | 28(71.8) | | 27 (65.9) | | 158 (79.2) | |
| Main place for health care | | | | | | | | | |
| Government hospital | 1282 (65.6) | 174 (62.1) | 0.39 | 25(64.1) | 0.89 | 24 (55.8) | <0.001 | 125 (62.5) | **0.48** |
| Private practice | 601 (30.8) | 92 (32.9) | | 13(33.3) | | 10 (24.4) | | 69 (34.5) | |
| Both | 71 (3.6) | 14 (5.0) | | 1(2.6) | | 7(17.1) | | 6(3.0) | |

3.2.5 Self-reported general and oral health status and preterm birth

The general health status of mothers showed a statistically significant association with preterm birth. Among women with term deliveries, 51.6% rated their health as *good*, 19.3% as *fair*, and 10.4% as *excellent*. In contrast, among preterm births, a higher proportion of women reported *poor* (10.4%) or *fair* (27.5%) health, whereas fewer reported *good* (40.4%). This trend indicates that women who perceive their general health as below average have a greater likelihood of preterm delivery. When analyzed by subtypes, very preterm birth (VPTB) also demonstrated a significant relationship (p = 0.01). Women in this group most frequently described their health as fair (39 %), while those with excellent health ratings were least represented (9.8 %).

The general health status of fathers did not differ significantly between the term and preterm groups (p = 0.16). The majority of fathers were rated as having good or very good health ( 85 % combined). Only 3 % of term and preterm fathers were rated as poor. No significant differences were found between subgroups of preterm birth (p > 0.05).

Table 11 – The association between oral and general health and preterm birth

| Variables | Term (n=1955) | preterm (n=280) | P | EPTB (n=39) | P | VPTB (n=41) | P | MLPTB (n=200) | P |
|---|---|---|---|---|---|---|---|---|---|
| Self reported general health status of mother | | | | | | | | | |
| Poor | 85 (4.3) | 29 (10.4) | <0.001 | 7 (17.9) | 0.001 | 4 (9.8) | 0.01 | 18 (9.0) | 0.01 |
| Fair | 376 (19.3) | 77 (27.5) | | 12 (30.8) | | 16 (39.0) | | 49 (24.5) | |
| Good | 1008 (51.6) | 113 (40.4) | | 16 (41.0) | | 14 (34.1) | | 83 (41.5) | |
| Very good | 282 (14.4) | 29(10.4) | | 2 (5.1) | | 3 (7.3) | | 24 (12.0) | |
| Excellent | 204 (10.4) | 32(11.4) | | 2 (5.1) | | 4 (9.8) | | 26 (13.0) | |
| General health status of father | | | | | | | | | |
| Poor | 42 (2.1) | 9 (3.2) | 0.16 | 1 (2.6) | 0.16 | 1 (2.4) | 0.11 | 7 (3.5) | 0.27 |
| Fair | 239 (12.2) | 45 (16.1) | | 9 (23.1) | | 11 (26.8) | | 25 (12.5) | |
| Good | 954 (48.8) | 123 (43.6) | | 21 (53.8) | | 17 (41.5) | | 85 (42.5) | |
| Very good | 419 (21.4) | 56(20.4) | | 5 (12.8) | | 7 (17.1) | | 44 (22.0) | |
| Excellent | 301(15.4) | 47(16.8) | | 3 (7.7) | | 5 (12.2) | | 39 (19.5) | |
| Oral health problems | | | | | | | | | |
| Yes | 1009(51) | 160(57) | 0.08 | 18(46) | 0.4 | 21(51) | 0.8 | 121(61) | 0.02 |

Overall, 46.1% of participants reported no oral problems during pregnancy, whereas 53.9% reported at least one complaint. The most frequently reported conditions were: tooth pain (14.3%), Dental caries (11.1%), Gingival bleeding (9.4%), Tooth extraction (9.0%), and Deep cavity (6.3%). Less common complaints included bad breath (1.4 %), tooth loss (0.2 %), and multiple combined oral problems (2.2 %). These findings indicate that more than half of pregnant women experienced at least one oral condition during pregnancy. When stratified by pregnancy outcome, the prevalence of oral problems was higher among women with preterm birth (60.4 %) than among those with term birth (53.9 %). Among preterm deliveries, 21.4 % reported tooth pain, 14.9 % tooth extraction, 10.4 % gingival bleeding, and 8.6 % deep caries. In contrast, among term deliveries, the corresponding figures were 13.2%, 8.7%, 9.7%, and 5.7%, respectively. Although the absolute differences were moderate, they demonstrated a consistent pattern of poorer oral health among preterm cases. Cross-tabulation of overall oral status (normal vs. problem) with pregnancy outcomes showed that 57.1% of women with preterm pregnancies had at least one oral problem, compared with 51.6% of women with term pregnancies.

3.2.6 The multivariable analysis of the factors

Multivariable logistic regression models were used to examine the association between maternal characteristics and the risk of preterm birth. The results show that a history of preterm birth was associated with the highest risk of recurrent PTB. Women with this risk factor have almost six times higher risk of delivering preterm again compared to those who never experienced PTB. Other at-risk mothers have characteristics such as being a first-time mother (OR = 1.7, 95% CI: 1.5–4.2), previous adolescent pregnancy (OR = 1.3, 95% CI: 1.1–1.5), and Oral health problems during pregnancy (OR = 1.10, 95% CI: 1.02–1.20). The group with higher pre-pregnancy BMI and good self-reported maternal health (OR = 0.8; 95% CI: 0.7–0.9) had a lower risk, as shown in Figure 8.

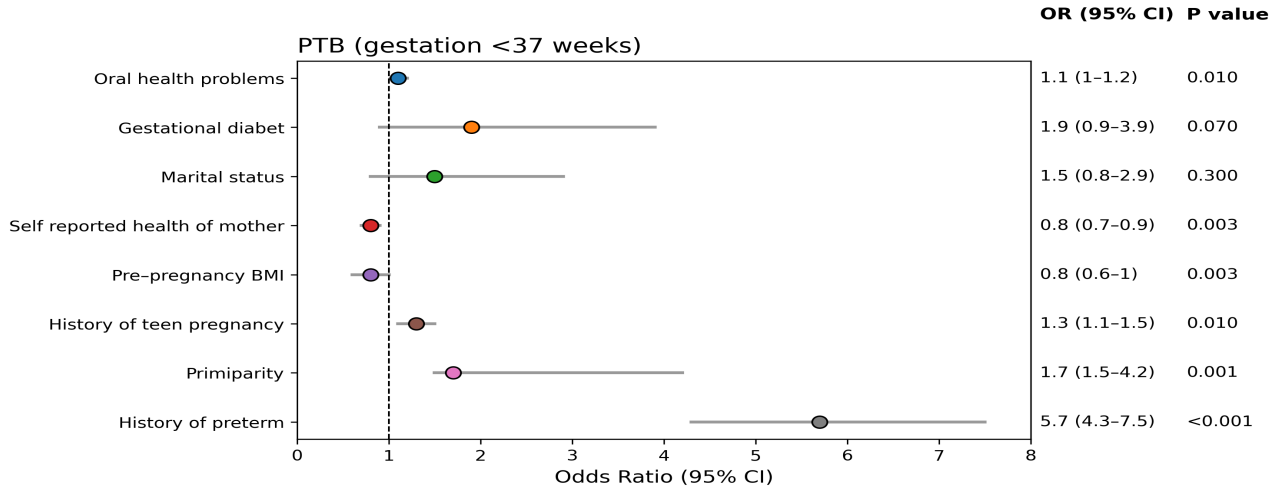


Figure 8 – Multivariable Logistic Regression of Maternal Determinants of PTB

The regression results indicated that the determinants of preterm birth are heterogeneous across gestational age subgroups, as shown in Table 12. There was no meaningful association between pre-pregnancy BMI and the risk of either extremely preterm birth (EPTB) or very preterm birth (VPTB). Similarly, maternal self-reported general health and parity did not significantly contribute to the risk of moderate-to-late preterm birth (MLPTB). In contrast, women who were divorced, widowed, or separated had five times the risk of EPTB. Women who were first-time mothers and had gestational diabetes had a four to fivefold increased risk of VPTB, respectively. Meanwhile, women with a low pre-pregnancy BMI and those with a history of teenage pregnancy had about twice the risk of MLPTB.

Table 12 – Association between maternal determinants and PTB subgroup

| | EPTB (gestation<28 week) | | |
|---|---|---|---|
| Variables | Adjusted OR | 95% CI | P |
| History of preterm | 4.4 | 2.2-8.5 | 0<0.001 |
| Health of the mother | 0.6 | 0.4-0.8 | 0.001 |
| Marital status | 5.1 | 1.9-13.7 | 0.001 |
| | VPTB (28≤gestation<32 week) | | |
| Variables | Adjusted OR | 95% CI | P |
| History of preterm | 4.5 | 2.3-9.0 | 0.001 |
| Primiparity | 3.8 | 1.9-7.7 | 0.001 |
| History of teen pregnancy | 0.1 | 0.02-0.7 | 0.02 |
| Self reported health of mother | 0.7 | 0.5-0.9 | 0.02 |
| Gestational diabet | 5.2 | 1.7-16.3 | 0.005 |
| | MLPB (32≤gestation<37 week) | | |
| Variables | Adjusted OR | 95% CI | P |
| History of preterm | 6.1 | 4.5-8.4 | 0<0.001 |
| Pre-pregnancy weight | 2.3 | 1.3-3.9 | 0.003 |
| History of teen pregnancy | 0.4 | 0.2-0.7 | 0.003 |
| Oral health problems | 1.1 | 1.0-1.2 | 0.02 |

### 3.2.7 Discussion of the results

The present cohort study highlights key maternal, social, and self-rated health factors associated with preterm birth (PTB) and its subtypes in Kazakhstan [27,p. 769]. The findings from our study were consistent with global evidence that a history of PTB was the strongest predictor of recurrence in our cohort, which supports the conclusion that women with prior PTB were nearly six times more likely to deliver preterm again, consistent with findings from Mercer et al. and large population-based analyses by Ananth et al. and colleagues [393-395]. Multiple systematic reviews similarly demonstrate a three- to sixfold increase in recurrence risk, particularly for moderate-to-late PTB [396]. Several maternal demographic factors in our study, teenage pregnancy, low pre-pregnancy BMI, and primigravidity, were significantly associated with PTB. These findings align with those from the NICHD U.S. cohorts, Scandinavian birth registries, and East Asian population studies, which demonstrate that young maternal age, low BMI, and primigravida status are associated with PTB risk [397-

399]. The weak association observed between maternal age and PTB is consistent with findings from Japan, Sweden, and the U.K., where maternal age has limited predictive value after controlling for confounders [400-401].

In our analysis, we also observed that distinct subtypes of preterm birth were associated with distinct maternal conditions [393,p. 1216]. For example, gestational diabetes was particularly associated with very preterm birth (VPTB). Similar patterns have been reported in cohort studies from Canada, Taiwan, and Australia, where gestational diabetes appears to play a greater role in earlier, medically indicated preterm delivery [402–404]. Conversely, preeclampsia was not significantly associated with PTB in our sample. However, some cohort studies have suggested that this association may be weaker in populations where severe hypertensive disorders are relatively uncommon or where antenatal care systems are highly effective in monitoring and managing maternal complications[405].

Most reported obstetric histories, without either miscarriage or abortion, showed significant associations with PTB. The findings are consistent with meta-analyses that found little or no independent effect after adjustment for confounders [406-407].

Social and economic factors, including education, employment, and income, were not significantly associated with PTB in our cohort [393,p. 1216]. Similar patterns have been documented in socially homogenous, high-literacy populations such as Singapore and Scandinavian countries [408-409]. However, housing instability emerged as a significant predictor of PTB, and marital status was strongly associated with EPTB, such that divorced or widowed women had a markedly higher risk of very early delivery. These findings are consistent with previous evidence showing that unstable living conditions disproportionately increase the risk of early PTB [410-411].

Self-rated health status was associated with an increased risk of PTB in our findings [393,p. 1216]. Women reporting tooth pain, caries, gingival bleeding, or requiring dental extraction were significantly more likely to experience PTB. Similar findings were reported in studies from Brazil, Turkey, China, and the United States, as well as in international meta-analyses [412-415]. These studies support the biological pathways by which periodontal inflammation, untreated caries, and periapical infections contribute to systemic inflammatory activation and microbial dissemination, thereby increasing the risk of PTB.

The cohort study provided important population-level information that the risk profile observed in Kazakhstan is similar to that in other countries. Still, it also exhibits distinctive elements likely attributable to local social and healthcare conditions. However, a nested case–control study was needed within the cohort to address several methodological limitations. The oral health status of the cohort was based on self-reported data, which are known to underestimate the actual disease burden, as many women adapt to chronic oral conditions and remain asymptomatic despite oral pathologies.

### 3.3 Result of case-control study

3.3.1 Sample characteristics

A total of 270 pregnant women with 90 spontaneous preterm and 180 term births underwent further oral health evaluation. Among the 90 singleton sPTB included in the study, 17 were extremely preterm, 37 were very preterm, and 36 were moderate to late preterm. The mean age of the pregnant women was 28.7 (SD=6.1) years, with no difference between cases and controls (p=0.921). The mean BMI of the participants was 24.0 (SD = 4.2) kg/$m^2$. No differences between cases and controls were observed when age (p=0.921) and pre-gestational BMI (p=0.094) were treated as continuous variables. Only 7% of women had less than 12 years of education. At the same time, 36% of women were unemployed. All the women were ethnic Kazakhs. None reported smoking or consuming alcohol. However, 20% of the participating women reported being exposed to tobacco because of having a smoking family member [28,p. 901].

3.3.2 Oral health status of the sample

The oral health examination revealed that 66% of participants had at least one untreated carious lesion requiring restorative, endodontic, or extraction treatment, depending on disease severity. Nearly half (49%) of the women had at least one missing posterior tooth, and none had prosthetic replacements, whereas 40% had at least one restored tooth. The mean Decayed, Missing, and Filled Teeth (DMFT) index was 4.33 ± 2.31, composed of decayed (D) = 1.46 ± 1.83, missing (M) = 1.51 ± 2.10, and filled (F) = 1.35 ± 1.42 components.

Regarding periodontal status, 51.6% of the women presented with clinical signs compatible with gingivitis, and 31.1% with periodontitis. Among participants with periodontitis, the majority (75%) were categorized as Stage I–II (initial to moderate periodontitis), whereas a smaller proportion (25%) met criteria for Stage III–IV (severe to advanced periodontitis). The mean probing depth (PD) varied across different tooth types, as shown in Figure 9. The mean probing depth (PD) across all examined sites was 3.5 ± 0.9 mm.

Regarding gingival inflammation, the percentage of bleeding-on-probing (BOP) sites varied widely among participants. According to established clinical thresholds, 33% of women had BOP <10%, indicating localized gingival inflammation; 48% had BOP between 10–30%, reflecting moderate gingival involvement; and 19 % exhibited BOP >30%, consistent with generalized gingival inflammation. The overall mean percentage of BOP sites was 49.0 ± 20.3%, indicating a predominance of moderate bleeding tendency in the study population.

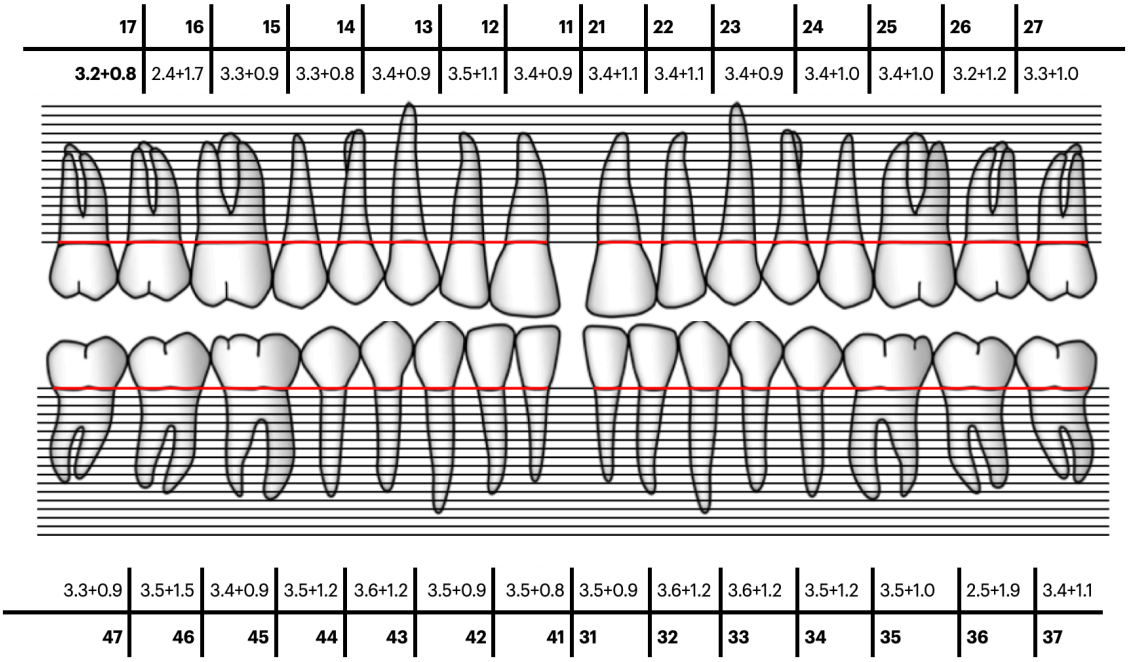


Figure 9 – Mean probing depth (PD) across different tooth types

Based on PSR, half of the participants demonstrated signs of periodontal involvement. Scores of 0–1 were observed in 44% of women, score 2 in 25%, score 3 in 11%, and score 4 (probing depth >5.5 mm) in 20.0% (figure10).

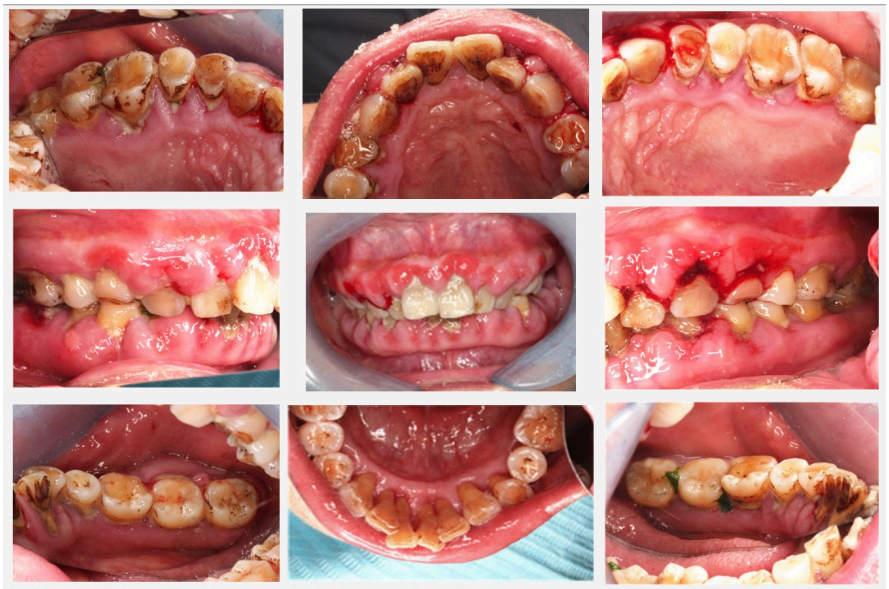

Figure 10 – Clinical Presentation of Gingival Inflammation, Calculus Accumulation, and Periodontal Breakdown Among Pregnant Women in the Study Population

Among the 270 pregnant women examined, 46% reported visiting a dentist within the past 12 months. Of these, 15% sought care for preventive purposes, whereas 31% presented with symptoms such as pain, bleeding, or visible caries. The remaining 54% reported not having attended a dental clinic during pregnancy. Regarding self-perceived oral symptoms, 20% of women reported experiencing dental pain, 16% noted spontaneous gingival bleeding during brushing or eating, and 15% noticed visible dental cavities.

3.3.3 The association between oral health status and preterm birth

Statistically significant differences between cases and controls were observed for several sociodemographic and oral health variables. Women with a history of preterm birth, miscarriage, or abortion were significantly more represented among the preterm group compared to term controls.

Table 13 – Descriptive characteristics of pregnant women's socioeconomic and obstetric background between group

| Variable | | Term (n) | Preterm (n) | P-value |
|---|---|---|---|---|
| Age | Mean | 28.8±5.5 | 28.8±6.9 | 0.1 |
| BMI | Mean | 23.6±4.4 | 24.5±3.8 | 0.09 |
| New born sex | Girl | 105(58%) | 49(54%) | 0.6 |
| | Boy | 75(42%) | 41(46%) | |
| Education | Secondary | 70 (38.9%) | 48 (53.3%) | 0.034 |
| | Higher | 110 (61.1%) | 42 (46.7%) | |
| Employment | House wife | 61 (33.9%) | 35 (38.9%) | 0.719 |
| | Employed | 117 (65.0%) | 54 (60.0%) | |
| | Student | 2 (1.1%) | 1 (1.1%) | |
| Income | Less | 30 (16.7%) | 20 (22.2%) | 0.533 |
| | Moderate | 101 (56.1%) | 48 (53.3%) | |
| | Higher | 49 (27.2%) | 22 (24.4%) | |
| Number Pregnancy | Mean | 3.06+1.88 | 3.21+2.07 | 0.5 |
| History Preterm | No | 178 (98.9%) | 64 (71.1%) | 0.001 |
| | Yes | 2 (1.1%) | 26 (28.9%) | |
| miscarriage | No | 129 (71.7%) | 51 (56.7%) | 0.02 |
| | Yes | 51 (28.3%) | 39 (43.3%) | |
| Abortion | No | 143 (79.4%) | 60 (66.7%) | 0.03 |
| | Yes | 37 (20.6%) | 30 (33.3%) | |

There were significant differences in oral health status among preterm mothers across oral health parameters. Preterm mothers reported a higher prevalence of self-perceived tooth pain and clinically diagnosed periodontitis. The distribution of periodontitis stages according to the 2017 World Workshop criteria also differed significantly between the groups, with higher proportions of Stages II and III among preterm cases. Moreover, the mean bleeding-on-probing (BOP) percentage,

periodontal screening and recording (PSR) scores, and mean probing depth (PD) were all significantly greater in the preterm group than in the term group. These findings indicate that poorer periodontal health and adverse reproductive history are significantly associated with spontaneous preterm birth in the studied sample.

Table 14 – Descriptive characteristics of pregnant women's oral health utilization and self-reported status between groups

| Variable | | Term (n) | Preterm (n) | P-value |
|---|---|---|---|---|
| Dental utilization | Never | 99 (55.0%) | 46 (51.1%) | 0.821 |
| | During pregnancy | 54 (30.0%) | 30 (33.3%) | |
| | Before pregnancy | 27 (15.0%) | 14 (15.6%) | |
| Pain | No | 152 (84.4%) | 63 (70.0%) | 0.009 |
| | Yes | 28 (15.6%) | 27 (30.0%) | |
| Bleeding | No | 153 (85.0%) | 73 (81.1%) | 0.522 |
| | Yes | 27 (15.0%) | 17 (18.9%) | |
| Cavity | No | 152 (84.4%) | 77 (85.6%) | 0.952 |
| | Yes | 28 (15.6%) | 13 (14.4%) | |
| Sugar rich diet | No | 147 (81.7%) | 77 (85.6%) | 0.529 |
| | Yes | 33 (18.3%) | 13 (14.4%) | |
| brush | No | 45 (25.0%) | 16 (17.8%) | 0.237 |
| | Yes | 135 (75.0%) | 74 (82.2%) | |

There were significant differences in oral health status among preterm mothers across oral health parameters. Preterm mothers reported a higher prevalence of self-perceived tooth pain and clinically diagnosed periodontitis. The distribution of periodontitis stages according to the 2017 World Workshop criteria also differed significantly between the groups, with higher proportions of Stages II and III among preterm cases. Moreover, the mean bleeding-on-probing (BOP) percentage, periodontal screening and recording (PSR) scores, and mean probing depth (PD) were all significantly greater in the preterm group than in the term group. These findings indicate that poorer periodontal health and adverse reproductive history are significantly associated with spontaneous preterm birth in the studied sample.

Table 15 – Descriptive characteristics of pregnant women's clinical oral health status between groups

| Variable | | Term (n) | Preterm (n) | P-value |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| Dental caries | DMFT | 4.5±2.3 | 4.0±2.2 | 0.2 |
| | D | 1.4±1.7 | 1.6±1.9 | 0.4 |
| | M | 1.5±2.1 | 1.5±1.9 | 0.9 |
| | F | 1.4±1.5 | 1.3±1.4 | 0.7 |
| Periodontitis | No | 135 (75.0%) | 51 (56.7%) | 0.003 |

Continuation of table 15

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | Yes | 45 (25.0%) | 39 (43.3%) | |
| | Stage I | 24(13%) | 18(20%) | 0.03 |
| | Stage II | 11(6%) | 10(11%) | |
| | Stage III | 8(4%) | 8(9%) | |
| | Stage IV | 2(1%) | 3(3%) | |
| BOP | Less than 10% | 60 (33.3%) | 29 (32.2%) | 0.30 |
| | Between 10% -30% | 90 (50.0%) | 39 (43.3%) | |
| | More than 30% | 30 (16.7%) | 22 (24.4%) | |
| | Mean BOP site % | 46 ±19 | 55 ±19 | 0.001 |
| PSR | 0 | 8 (4.4%) | 0 (0.0%) | 0.001 |
| | 1 | 85 (47.2%) | 28 (31.1%) | |
| | 2 | 42 (23.3%) | 23 (25.6%) | |
| | 3 | 20 (11.1%) | 9 (10.0%) | |
| | 4 | 25 (13.9%) | 30 (33.3%) | |
| PD | Mean | 3.4 ±0.7 | 3.8 ±1.3 | 0.001 |

The multivariable logistic regression analysis identified several significant oral-health and obstetric predictors of preterm birth shown in Table 16. Women reporting dental pain during pregnancy (aOR 2.9, 95% CI 1.2–6.8) and those with higher PSR scores (aOR 3.3, 95% CI 1.6–6.6) or increased bleeding on probing (aOR 6.2, 95% CI 1.2–30.7) had markedly higher odds of preterm delivery, indicating that active inflammation and symptomatic oral disease are important contributors. A history of miscarriage was also associated with a twofold increased risk (aOR 2.1, 95% CI 1.1–4.1). The strongest predictor in the model was a previous preterm birth, which increased the risk nearly 69-fold (aOR 68.62, 95% CI 11.96–393.59). Healthy periodontal status (aOR 0.06, 95% CI 0.08–0.36) and higher DMFT scores (aOR 0.8, 95% CI 0.7–0.9) showed protective associations in this adjusted model, likely reflecting complex interactions between disease severity, dental treatment history, and measurement timing. Overall, the findings highlight the substantial contributions of inflammatory oral conditions and a history of reproductive events to the risk of preterm birth.

Table 16 – Association between pregnant women's socioeconomic background, health habits and oral health status to the PTB

| Variable | Adjusted OR | 95% CI | P-value |
|---|---|---|---|
| 1 | 2 | 3 | 4 |
| Periodontitis | 0.06 | 0.08–0.36 | 0.02 |
| Pain | 2.9 | 1.2-6.8 | 0.001 |
| DMFT | 0.8 | 0.7-0.9 | 0.01 |
| PSR | 3.3 | 1.6-6.6 | 0.001 |

Continuation of table 16

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Mean BOP site % | 6.2 | 1.2-30.7 | 0.02 |
| History Preterm | 68.62 | 11.96–393.59 | 0.0 |
| Miscarage | 2.1 | 1.1-4.1 | 0.03 |

### 3.4 Fusobacterium nucleatum and Preterm Birth

3.4.1 Fusobacterium nucleatum Detection

*F. nucleatum* DNA was detected in saliva samples of 65.9% of participants and in both saliva and placental tissues in 9.6% of cases. Co-detection in both sites was observed in 9.6% of participants and was significantly more frequent among those who experienced preterm birth (61.5% of co-detected cases, $p = 0.02$). Binary logistic regression showed that co-detection of F. nucleatum in both saliva and placenta was independently associated with increased odds of preterm birth (adjusted OR 3.68, 95% CI: 1.59–8.48, $p < 0.01$), even after controlling for socioeconomic and clinical variables.

3.4.2 Machine Learning Model

A stacked ensemble classifier was developed to predict birth outcomes (term vs. preterm) using maternal characteristics, oral health indicators, and microbiological variables. Performance was evaluated on the held-out test dataset.

Across models, test-set accuracy ranged from approximately 0.73-0.80, with the CatBoost classifier performing best overall (Accuracy ≈ 0.80, F1-score ≈ 0.80, $\kappa \approx 0.48$). The stacked ensemble achieved comparable performance. Precision–recall analysis demonstrated moderate discriminative ability for both outcome classes, with area-under-curve (AUPRC) values of 0.77 for Class 0 and 0.71 for Class 1, and a micro-average AUPRC of 0.75. Receiver operating characteristic (ROC) analysis yielded AUC values of 0.73 for both classes, with a micro-average AUC of 0.80.The model classification performance is shown in Figure 11.

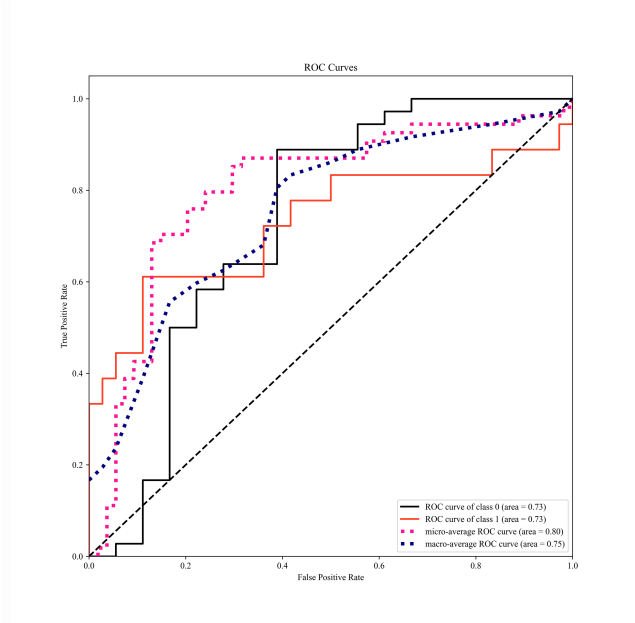


Figure 11 – Precision–Recall and Receiver Operating Characteristic (ROC) Curves for the Machine-Learning Model Predicting Birth Outcomes

The stacked classifier demonstrated moderate discriminative ability between preterm and term birth outcomes. The confusion matrix shown that 94 of 100 women with term deliveries were correctly classified, whereas 39 of 100 preterm cases were correctly identified, indicating higher accuracy for predicting term birth than preterm birth. This pattern is expected in population-based cohorts where preterm birth is less frequent than term delivery (figure 12).

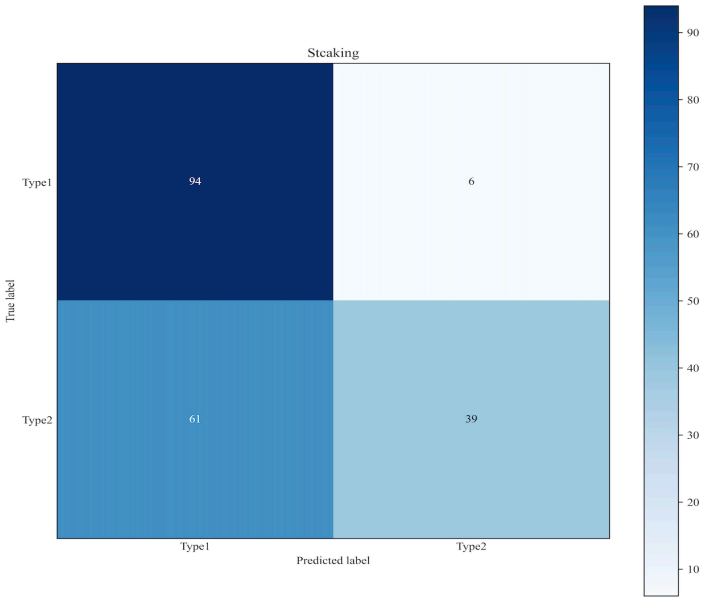


Figure 12 – Confusion Matrix for the Stacked Machine-Learning Classifier

To assess the relative contribution of each base classifier within the stacked ensemble model, SHAP analysis was applied at the model level. The stacked ensemble assigned the highest contribution to the CatBoost classifier, followed by Random Forest and AdaBoost, while XGBoost, LightGBM, and Gradient Boosting contributed to a lesser extent (figure 13). This indicates that tree-based gradient-boosting approaches, particularly CatBoost, provided the strongest predictive signal for the final model output.

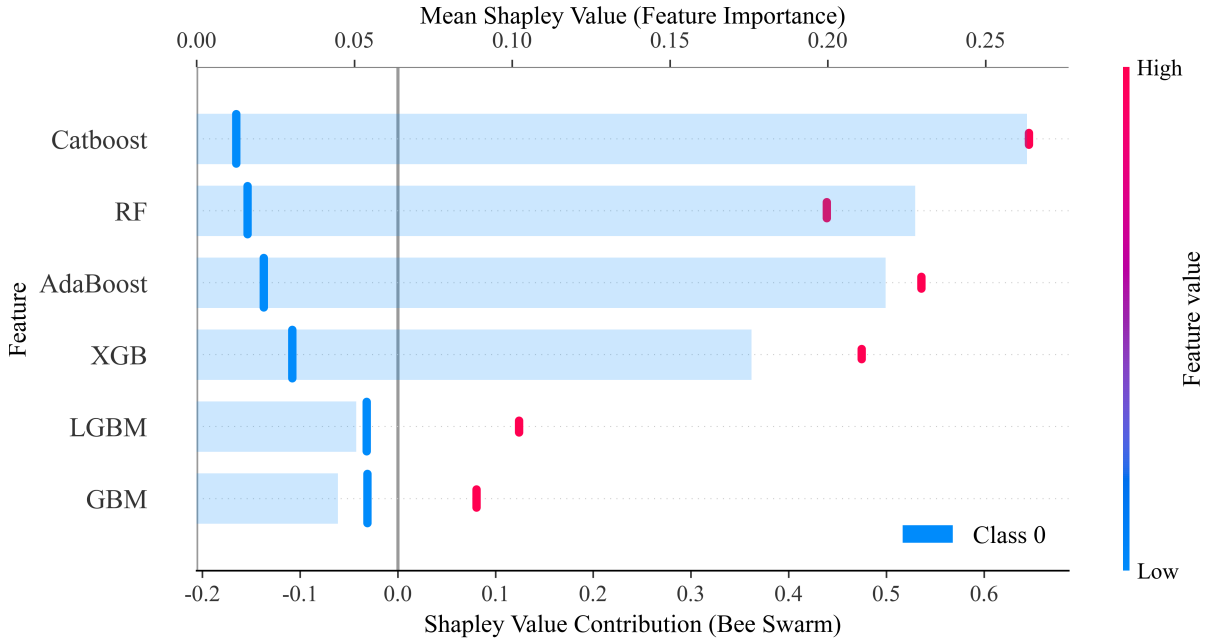


Figure 13 – SHAP Feature Contribution Analysis for the Stacked Ensemble Model Predicting Preterm Birth

To better understand which factors were most influential in the machine-learning predictions, we applied SHAP (Shapley Additive Explanations) analysis to the stacked ensemble model. The SHAP feature-importance plot (figure X) summarises the average contribution of each predictor to the classification of birth outcomes. Maternal age emerged as the strongest overall contributor, followed closely by a previous history of preterm birth. This means that, across the dataset, these two factors consistently had the greatest impact on whether the model classified a pregnancy as preterm or term.Oral and general health characteristics also played an important role. periodontal screening scores (PSR), which indicate poorer periodontal condition, and higher maternal BMI were both associated with increased influence on the model output. Self-reported tooth pain and a prior miscarriage contributed meaningfully as well, suggesting that women experiencing oral discomfort or previous pregnancy loss may form a clinically important subgroup. The cumulative burden of dental disease, as reflected by the DMFT index, was also among the higher-ranking predictors.

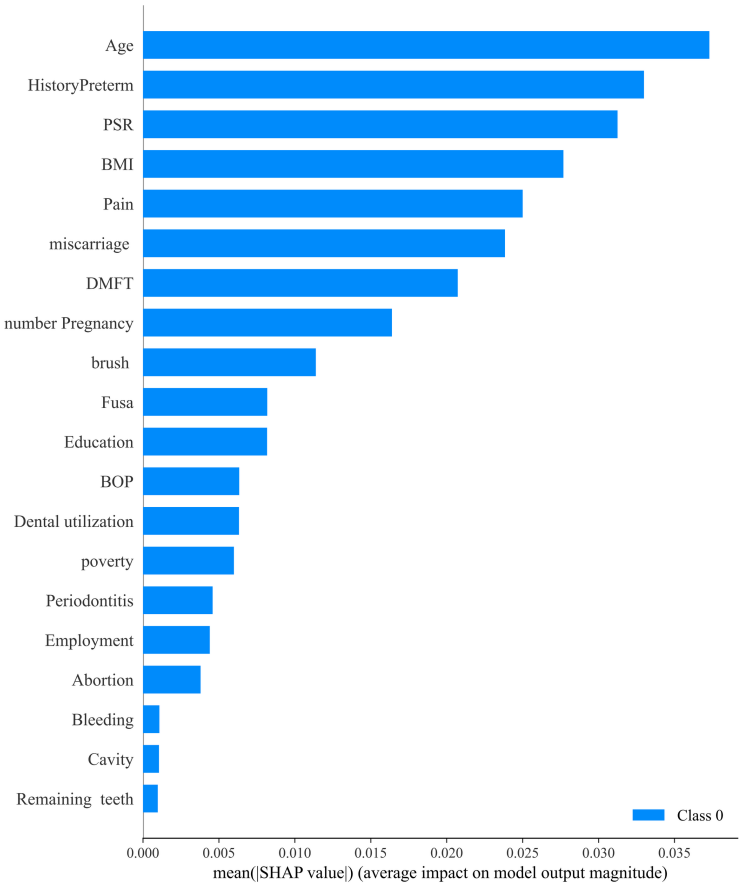


Figure 14 – SHAP Feature Importance Plot for the Stacked Ensemble Model Predicting Preterm Birth

To illustrate how individual-level risk patterns were represented in the model, SHAP force plots were generated for sample cases. These plots show how specific features increased or decreased the predicted probability of preterm birth for a given woman. In the example of a term delivery (figure 15), Blue bars indicate predictors that reduced the probability of preterm birth, while pink bars indicate predictors that increased risk. In this example, the baseline probability of preterm birth was approximately 30%. The model prediction was reduced to 18% after accounting for individual-level characteristics. The main protective influences were favourable periodontal health (PSR score = 1), absence of miscarriage or previous preterm birth, and normal BMI. These factors outweighed the modest risk-increasing effects of tooth pain and suboptimal brushing frequency. Overall, this case demonstrates how oral and reproductive health characteristics interact to influence predicted preterm birth risk.

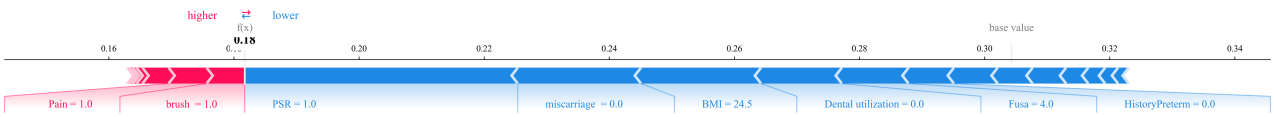


Figure 15 – SHAP Decision Plot for a Term Birth Case

In contrast, shown in figure 16, the baseline probability of preterm birth (approximately 30%) increased to approximately 70% after adjusting for individual characteristics. The largest contributors to increased risk were indicators of poor periodontal health, including a high PSR score and the presence of periodontitis, as well as a high DMFT index reflecting cumulative dental disease. Younger maternal age and lower educational level also contributed to a higher predicted risk. Although the absence of miscarriage conferred some protective effect, this effect was relatively small. This case illustrates how unfavourable oral health indicators and social vulnerability can combine with maternal demographic factors to increase the likelihood of preterm birth.

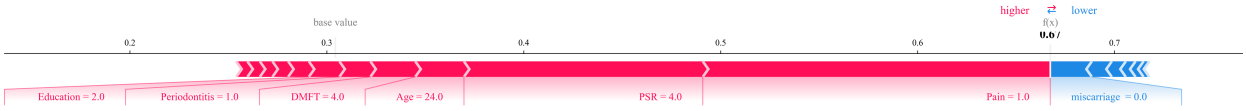


Figure 16 – SHAP Decision Plot for a Preterm Birth Case

To further interpret the stacked ensemble classifier, SHAP values were calculated for all predictors. The bee-swarm plots illustrate the relative contributions and directions of each variable in predicting term and preterm birth. Predictors located further from zero exert greater influence on the model output. Across both classes, maternal age and a previous history of preterm birth showed the largest SHAP magnitudes, indicating that these variables consistently had the strongest impact on risk classification. Higher PSR scores and greater cumulative dental disease burden (DMFT index) were also associated with substantial positive SHAP values, indicating that poorer periodontal status and more extensive dental pathology increased the probability of preterm birth. Maternal BMI and self-reported tooth pain contributed an additional positive signal to the model, suggesting that both metabolic status and symptomatic oral disease were relevant risk indicators.

Reproductive and behavioural factors, including history of miscarriage, parity, and toothbrushing frequency, showed a moderate influence. At the same time, socioeconomic measures such as education, employment, and poverty contributed to a lesser but detectable extent. Notably, the model incorporated multiple risk domains rather than relying on a single dominant factor, reflecting the complex and multifactorial nature of preterm birth. The consistent contribution of clinically assessed oral health variables, alongside recognised obstetric predictors, supports the biological plausibility of an independent association between maternal oral disease burden and adverse pregnancy outcomes.

In the SHAP bee-swarm analysis for term birth, the variables with the strongest stabilising influence toward a term delivery were maternal age, history of preterm birth, PSR score, and BMI, shown in Figure 17. For these predictors, most points clustered close to zero but with clear gradients indicating the direction of effect. Higher

periodontal screening scores and higher BMI values were associated with a lower probability of term birth. In contrast, younger maternal age and the absence of previous preterm birth were associated with greater likelihood of delivering at term. Self-reported tooth pain and dental disease burden (DMFT) also showed measurable influence, with symptomatic or untreated dental conditions shifting the prediction away from the term category. Reproductive and social factors, such as parity, history of miscarriage, and education, contributed more modestly. Taken together, the model suggests that adverse oral and systemic health markers weaken the prediction of a term birth, whereas favourable maternal and reproductive profiles support it.

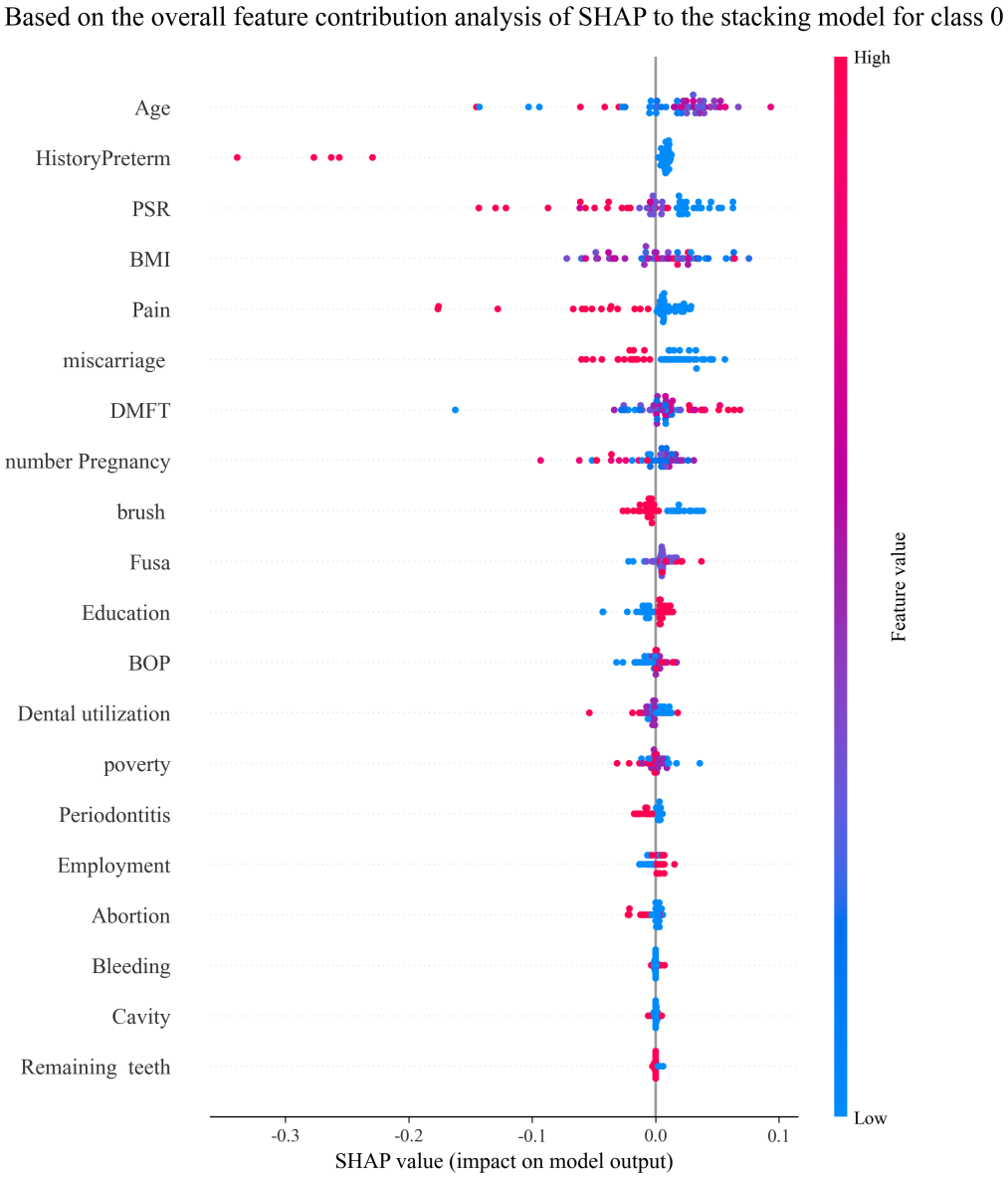


Figure 17 – SHAP Bee-Swarm Plot for Term Birth

The SHAP bee-swarm plot for PTB demonstrates a mirror-symmetric relationship in figure 18, in which many of the same predictors exert opposite directional effects. Higher PSR scores, older maternal age, greater dental disease burden, and the presence

of tooth pain were strongly associated with increased probability of preterm birth. A previous history of preterm delivery again emerged as one of the most influential predictors, consistently shifting model output toward the preterm category. BMI also contributed positively to preterm birth risk, particularly at higher values. In contrast, women with lower periodontal indices, fewer decayed or missing teeth, and no prior obstetric complications were more likely to be classified as term. Behavioural indicators, such as brushing frequency, exerted secondary effects, whereas socioeconomic and service-use measures contributed to a lesser extent. These results reinforce the observation that oral disease severity and prior obstetric vulnerability play a central role in shaping preterm birth risk within the model.

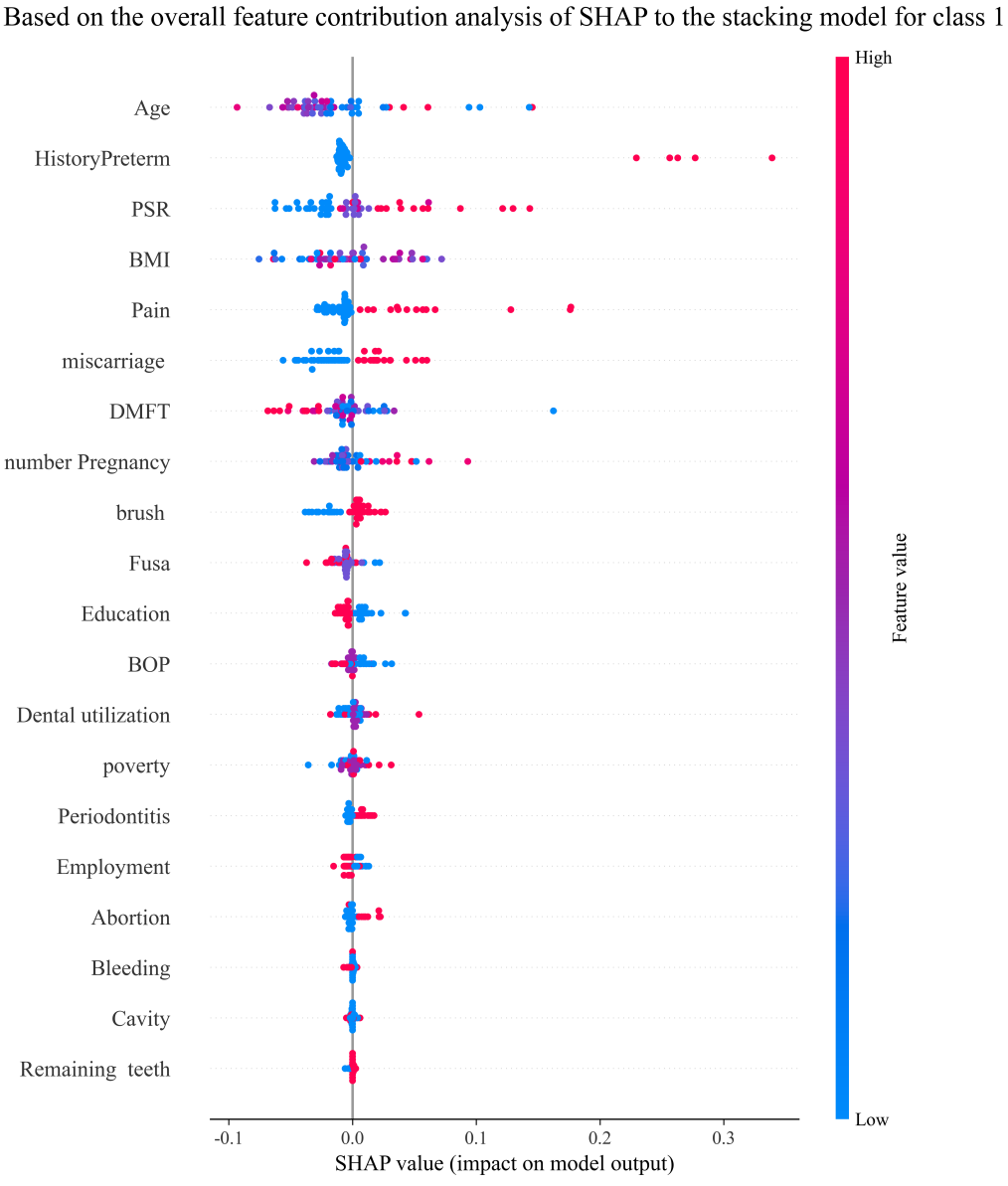


Figure 18 – SHAP Bee-Swarm Plot for Term Birth

3.4.3 Common Risk Factor Approach (CRFA) Analysis

The combined correlation and network analysis showed that oral-health status, maternal characteristics, and preterm birth were closely interconnected. Periodontitis was strongly linked with preterm birth and with signs of oral inflammation such as bleeding gums, pain, and plaque buildup. At the same time, women with periodontal disease were more likely to come from socially or economically disadvantaged backgrounds.Preterm birth showed overlapping associations with many of these variables. It was connected not only with periodontitis, but also with maternal age, previous preterm birth, miscarriage history, and socioeconomic disadvantage, shown in figure 19.

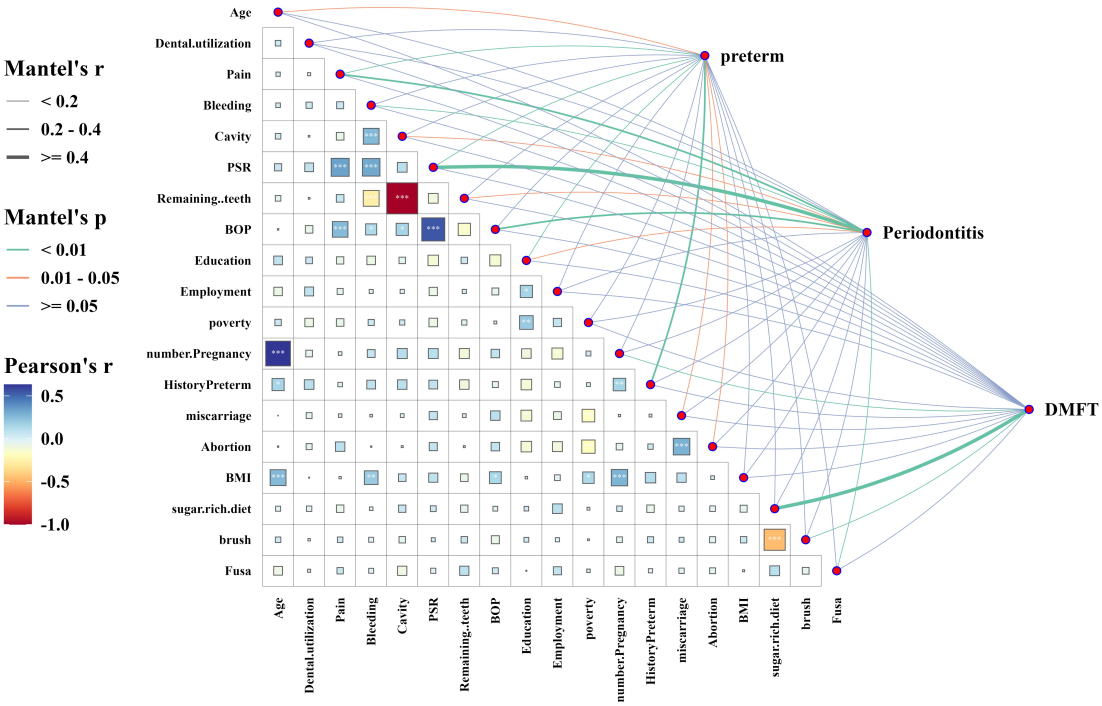


Figure 19 – Common Risk Factor Network Linking Oral health status, Maternal Characteristics, and Preterm Birth

3.4.4 Discussion of the results

Despite universal access to antenatal care and free emergency dental services, our nested case–control study indicates that the oral health status of pregnant women in Kazakhstan is concerning, with two-thirds having at least one untreated carious lesion and almost one-third meeting criteria for periodontitis [364,p. 412]. The burden of oral diseases is comparable to the findings of studies conducted in Latin America, Eastern Europe, and Asia, where 50–80% of pregnant women present with active caries and

30–40% with periodontitis or advanced gingivitis [248,p. 1125]. Similar to studies from Brazil, Turkey, and China, we found a high prevalence of bleeding on probing and shallow–moderate pockets, indicating widespread chronic gingival inflammation rather than periodontitis [249,p. 495].

Our findings that periodontal inflammation, reflected by higher PSR scores, increased probing depths, and marked bleeding on probing, is associated with significantly higher odds of spontaneous preterm birth are consistent with the international literature, which have reported that women with periodontitis have approximately 1.5–2.0 times higher risk of PTB compared with periodontally healthy women, even after adjustment for major confounders [392,p. 13]. The strong associations we observed for BOP and oral pain support the hypothesis that active inflammatory burden may be particularly relevant to the pathophysiology of PTB through systemic cytokine release, bacteremia, and placental inflammatory activation [372,p. 420]. This is consistent with reports showing that sites with high BOP and deep pockets are more strongly associated with elevated systemic inflammatory markers and adverse obstetric outcomes than with treated or quiescent periodontal lesions [372,p. 420].

The apparent protective effects of higher DMFT scores and clinically healthy periodontal status in our adjusted models warrant cautious interpretation. Similar "paradoxical" findings have been reported in some studies, in which women with more filled teeth or a history of dental treatment appeared to have a lower PTB risk than those with fewer recorded lesions [374,p. 1428]. One plausible explanation is that the higher DMFT in our sample partly reflects greater lifetime dental care utilization. In contrast, women with low DMFT but high levels of untreated disease and pain may be under-represented by this index. In other words, DMFT may serve as a proxy for past access to dental services rather than for current inflammatory load [368,p. 203]. Residual confounding by socioeconomic status, health literacy, or timing of dental treatment relative to pregnancy may also contribute. Future analyses that distinguish among decayed, missing, and filled components, and incorporate radiographic data, could help clarify these relationships [374,p. 1428].

The robust association between prior preterm birth and spontaneous PTB in this nested sample (aOR = 69, with a wide confidence interval) is directionally consistent with large registry-based studies from North America, Europe, and Australia, which consistently report 3–6-fold recurrence risks [396, p. 154]. The larger point estimate in our study likely reflects the relatively small sample size and concentration of recurrent PTB among high-risk women referred to tertiary care. Still, it reinforces the central role of obstetric history as a dominant predictor. The additional association we observed between a history of miscarriage and PTB is consistent with findings from some international cohorts. However, meta-analyses indicate heterogeneity depending on how miscarriage is defined and adjusted for [407,p. 7077].

Machine-learning interpretation using SHAP values provided additional insight into these associations. Age, previous preterm birth, and indicators of active periodontal inflammation (PSR, bleeding, pain) were consistently ranked among the strongest contributors to preterm birth prediction, alongside BMI and miscarriage

history. Oral-health behaviours and microbiological exposure contributed to a lesser extent, but still meaningfully. These results reinforce the regression findings and highlight that oral disease severity interacts with other maternal health factors in a multidimensional manner, supporting the biological plausibility of the observed relationships.

The Common Risk Factor Approach analysis further demonstrated that poor oral health and preterm birth frequently arise from shared social and behavioural determinants. Lower education, unemployment, and poverty were linked simultaneously with periodontitis, higher DMFT scores, and preterm birth. This suggests that disadvantage may act through multiple parallel pathways — including inflammation, reduced access to timely treatment, psychosocial stress, and nutritional imbalance — ultimately increasing obstetric vulnerability.

A major strength of this work is the integration of complementary study designs. The prospective cohort allowed assessment of self-reported oral symptoms during pregnancy, while the nested case–control study provided clinically verified periodontal diagnoses. Machine-learning analysis and CRFA added further depth by clarifying interaction structure and shared determinants. However, the case–control sample size was modest, leading to wide confidence intervals for some predictors.

Together, these findings suggest that in Kazakhstan, where smoking and alcohol use in pregnancy are uncommon [360,p. 2], oral inflammation and reproductive history are particularly important contributors to preterm risk. This pattern is similar to global evidence but reflects local risk structures, including service access patterns and social conditions. The results therefore support routine oral-health assessment, education, and timely referral during antenatal care, in line with international guidance [371,p. 203].

# CONCLUSION

The findings of this dissertation consistently support the hypothesis that compromised oral health is associated with an increased risk of preterm birth. Through a combination of systematic review, cohort and case-control studies, the study provides comprehensive evidence that maternal oral health status can significantly influence pregnancy outcomes, with implications for both clinical practice and public health policy.

The findings of this systematic review and meta-analysis provide strong and consistent evidence that maternal oral diseases are associated with an increased risk of preterm birth. Across 29 studies, periodontitis was associated with nearly a two-fold higher risk of preterm delivery (OR = 1.81; 95% CI: 1.60–2.03; $p < 0.001$), while periapical infection demonstrated a similarly elevated risk (OR = 2.14; 95% CI: 1.43–3.20; $p < 0.05$). Although studies assessing dental caries showed substantial heterogeneity ($I^2 = 92\%$), the pooled estimate indicated that women with preterm birth had significantly higher DMFT scores (mean difference = 1.56; 95% CI: 0.28–3.41), reflecting a greater burden of untreated or chronic dental disease. Taken together, these results support a clear pattern in which inflammatory oral conditions—whether periodontal, carious, or periapical in origin—are linked to adverse pregnancy outcomes. The overall evidence supports the biological plausibility of oral–systemic inflammatory pathways contributing to spontaneous preterm birth. It underscores the importance of integrating oral health into prenatal care strategies, particularly in populations with a high burden of dental disease.

The findings of cohort study confirm that recurrent PTB history, pre-pregnancy weight, reproductive and social stability, perceived health, and oral health status are key maternal determinants of preterm birth in this Kazakhstani cohort.According to our findings, a previous history of preterm birth was the strongest predictor, increasing recurrence risk by four- to six-fold across all PTB subtypes (EPTB: aOR 4.4, $p<0.001$; VPTB: aOR 4.5, $p=0.001$; MLPTB: aOR 6.1, $p<0.001$). Pre-pregnancy weight was also important, with extremes of weight significantly associated with PTB ($p=0.002$) and, specifically, with MLPTB (aOR 2.3, $p=0.003$). Reproductive factors—including primigravidity (overall $p=0.03$; VPTB aOR 3.8, $p=0.001$) and teenage pregnancy (MLPTB aOR 0.4, $p=0.003$)—were significant contributors. Indicators of social stability showed notable effects: housing instability was associated with PTB ($p=0.02$), and divorced/widowed status increased the risk of EPTB more than five-fold (aOR 5.1, $p=0.001$). Perceived maternal health was strongly associated with PTB ($p<0.001$); poorer health was associated with increased risk across subtypes. Finally, oral health status showed a robust association with PTB ($\chi^2=83.4$, $p<0.001$), with a significant linear trend indicating higher PTB likelihood as oral problems increased ($p=0.002$).

The findings of case control study support the study objective by demonstrating that periodontal disease, inflammatory oral conditions, and microbiological dysbiosis—combined with maternal reproductive history, perceived health, and social vulnerability—are key determinants of spontaneous preterm birth in this Kazakhstani population. Clinically diagnosed periodontitis was substantially more common among

preterm cases (43.3% vs. 25.0%, p=0.003), and markers of periodontal inflammation—including mean BOP (55% vs. 46%, p<0.001), higher PSR scores (p=0.001), and greater probing depth (3.8 mm vs. 3.4 mm, p<0.001)—were all significantly elevated in women who delivered preterm. Symptomatic disease, such as dental pain, nearly tripled PTB odds (aOR 2.9; 95% CI 1.2–6.8), while miscarriage history also increased risk twofold (aOR 2.1; 95% CI 1.1–4.1). The strongest predictor was a previous preterm birth, which increased the odds of recurrence by almost 70-fold (aOR 68.62; 95% CI 11.96–393.59). Biological evidence further strengthened these findings: Fusobacterium nucleatum detected concurrently in saliva and placenta increased PTB odds more than threefold (aOR 3.68; 95% CI 1.59–8.48, p<0.01). Advanced machine-learning analysis identified maternal age, history of PTB, PSR, BMI, pain, and F. nucleatum as top predictors of earlier gestational categories, confirming that inflammatory periodontal burden and microbial dysbiosis contribute meaningfully to risk. Finally, CRFA network analysis demonstrated that oral diseases cluster with socioeconomic disadvantage, impaired oral hygiene behaviors, and obstetric vulnerability, illustrating a shared risk structure linking periodontal inflammation, maternal health, and adverse birth outcomes.

Taken together, the findings confirm the multifactorial nature of preterm birth and identify oral health as a modifiable contributor. Despite these, several limitations must be acknowledged. The case-control sample size, although powered adequately for primary analyses, limits broader generalizability. The study focused on a single microbial marker; broader metagenomic analysis could yield deeper insights. Finally, although causality cannot be definitively established from this design, the biological plausibility, combined with robust statistical associations, strengthens the validity of the conclusions.

In practical terms, this dissertation's findings emphasize the urgent need to incorporate oral health assessment and treatment into routine prenatal care in Kazakhstan. Although emergency dental care is available to pregnant women, the preventive aspect remains underutilized. Targeted health education, early identification of periodontal disease, and referral for dental treatment could serve as cost-effective strategies to improve birth outcomes. Public health programs should also address social determinants—such as education and access to care—to mitigate systemic disparities in maternal and child health.

In conclusion, this study contributes valuable, context-specific evidence to the growing body of research on the oral-systemic health connection. It confirms that poor maternal oral health—particularly periodontitis—is significantly associated with an increased risk of spontaneous preterm birth. The co-detection of *Fusobacterium nucleatum* in maternal saliva and placenta further supports a mechanistic link between oral infection and placental dysfunction. These findings underscore the importance of oral health as both a clinical and public health priority during pregnancy. Addressing it offers a promising pathway for reducing preventable preterm births and improving maternal and neonatal outcomes, especially in resource-constrained settings like Kazakhstan.

## PRACTICAL RECOMMENDATION

Based on the results of this dissertation, which demonstrated significant associations between maternal oral health disturbances and adverse pregnancy outcomes, it is recommended to incorporate oral health assessment and documentation of oral disease history into routine antenatal care protocols in the Republic of Kazakhstan. Early identification of periodontal inflammation and recognition of pre-existing oral conditions may contribute to the prevention of inflammation-mediated obstetric complications. Oral health should be considered a component of general maternal health rather than a pregnancy-only parameter. Therefore, it is advisable to integrate key oral health indicators, including history of periodontal disease, into a woman's longitudinal medical record within Kazakhstan's healthcare information systems.

It is advisable to introduce screening for oral and periodontal conditions at the first antenatal visit, consistent with national protocols emphasizing comprehensive history taking at pregnancy registration. Screening may be performed by obstetricians, general practitioners, or midwives using a brief standardized questionnaire combined with visual oral cavity inspection. Pregnant women presenting with gingival bleeding, tooth mobility, or visible signs of oral inflammation should be referred to a dental professional for comprehensive evaluation.

For ensuring continuity and preventive orientation of care, it is recommended to implement a "dental home" model, whereby each pregnant woman is linked to an assigned dental clinic or dentist responsible for monitoring oral health status, providing preventive counseling, and delivering pregnancy-safe dental treatment when clinically indicated. This model may strengthen interdisciplinary coordination and improve access to preventive dental services already supported within the state healthcare system.

In line with international guidance, oral health should be integrated into women's longitudinal medical history and antenatal care. Providers should review documented history of periodontal disease at the first antenatal registration, and dental professionals should perform periodontal evaluation during pregnancy when indicated. While periodontal diagnosis and non-surgical periodontal therapy are considered safe during pregnancy, the second trimester (14–28 weeks) is often preferred for elective comprehensive periodontal assessment and treatment. In cases of moderate or severe periodontal disease, it is recommended to establish interdisciplinary communication between dental and obstetric care providers, allowing integrated monitoring of maternal inflammatory status and individualized pregnancy management strategies.

It is recommended to develop and implement a digital documentation system integrating oral health indicators into routine maternal healthcare records. The inclusion of structured variables—such as history of periodontal disease, last dental visit, and findings from comprehensive periodontal charting—may improve continuity of care, facilitate interdisciplinary communication, and support early identification of oral health–related pregnancy risks. Digital recording of periodontal charting parameters is particularly important, as it enables objective assessment of periodontal

status, monitoring of disease progression, and evaluation of treatment outcomes over time.

In alignment with international clinical and public health guidelines (including recommendations from ACOG, ADA, and European periodontal consensus statements), national public health strategies are recommended to include structured educational materials for pregnant women and women of reproductive age. Such initiatives should address oral hygiene practices, reinforce the established safety of dental care during pregnancy, promote preventive dental attendance, and underscore the benefits of preconception oral health assessment.

## LIST OF REFERENCE


1 Romero R., Chaiworapongsa T., Korzeniewski S.J. The causes of preterm birth // Best Pract Res Clin Obstet Gynaecol. – 2018. – Vol. 52. – P. 3–15.

2 Vogel J.P., Chawanpaiboon S., Moller A.B. et al. The global epidemiology of preterm birth // Best Pract Res Clin Obstet Gynaecol. – 2018. – Vol. 52. – P. 3–12.

3 United Nations. Transforming our world: the 2030 Agenda for Sustainable Development. – New York, 2015.

4 Chawanpaiboon S., Vogel J.P., Moller A.B. et al. Global, regional, and national estimates of levels of preterm birth in 2014 // Lancet Glob Health. – 2019. – Vol. 7, №1. – P. 37–46.

5 Ohuma E.O., Moller A.B., Bradley E. et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis // Lancet. – 2023. – Vol. 402, №10409. – P. 1261–1271.

6 World Health Organization. WHO Research Priorities for Preterm Birth Prevention and Care 2021–2025. – Geneva, 2021.

7 UNICEF, WHO, World Bank Group, UN-DESA. Levels and Trends in Child Mortality 2022. – United Nations, 2023.

8 Cheong J.L., Anderson P.J. Long-term outcomes of preterm birth // Lancet. – 2020. – Vol. 396, №10253. – P. 1380–1390.

9 Franz A.P., Bolat G.U., Bolat H. et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: A meta-analysis // Pediatrics. – 2018. – Vol. 141, №1. – P. 20171645.

10 Crump C. An overview of mortality and long-term outcomes among infants born preterm // Clin Perinatol. – 2018. – Vol. 45, №2. – P. 325–340.

11 Twilhaar E.S., Wade R.M., Kieviet J.F. et al. Cognitive outcomes of children born extremely preterm: A meta-analysis // Pediatrics. – 2018. – Vol. 142, №1. – P. 20173021.

12 Pascal A., Govaert P., Oostra A. et al. Neurodevelopmental outcome of very preterm and very-low-birthweight infants at school age // Acta Paediatr. – 2018. – Vol. 107, №11. – P. 1886–1896.

13 Kajantie E., Strang-Karlsson S., Evensen K.A. et al. Adult outcomes of being born late preterm or early term // Semin Fetal Neonatal Med. – 2019. – Vol. 24, №1. – P. 66–75.

14 Carr H., Cnattingius S., Granath F. et al. Preterm birth and risk of heart failure up to early adulthood // J Am Coll Cardiol. – 2017. – Vol. 69, №21. – P. 2634–2642.

15 Crump C., Sundquist K., Winkleby M.A. et al. Preterm birth and early-term birth and risk of ischemic heart disease // Circulation. – 2019. – Vol. 139, №23. – P. 2828–2838.

16 Moskowitz C.S., Berrington de González A., Choi J. et al. Long-term health outcomes in individuals born preterm // Nat Rev Endocrinol. – 2019. – Vol. 15. – P. 147–158.

17 Phillips C., Velji Z., Hanly C., Metcalfe A. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis // BMJ Open. – 2017. – Vol. 7, №6. – P. 15402.

18 World Health Organization. Standards for Improving the Quality of Care for Small and Sick Newborns. – Geneva, 2020.

19 Boundy E.O., Dastjerdi R., Spiegelman D. et al. Kangaroo Mother Care and neonatal outcomes: A meta-analysis // Pediatrics. – 2016. – Vol. 137, №1. – P. e20152238.

20 Blencowe H., Krasevec J., de Onis M. et al. Preterm birth–associated burden in low- and middle-income countries // Lancet Glob Health. – 2019. – Vol. 7, №1. – P. 50–61.

21 Sakko Y., Turesheva A., Gaipov A. et al. Epidemiology of spontaneous pregnancy loss in Kazakhstan: national cohort analysis // Acta Obstet Gynecol Scand. – 2023. – Vol. 102, №12. – P. 1682–1693.

22 March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth – Progress Report 2023. – Geneva: WHO, 2023.

23 FIGO Working Group on Preterm Birth. International FIGO consensus guidelines on preterm birth prevention // Int J Gynaecol Obstet. – 2021. – Vol. 152, №1. – P. 3–13..

24 Mitrogiannis I., Evangelou E., Efthymiou A. et al. Risk factors for preterm birth: an umbrella review of meta-analyses of observational studies // BMC Med. – 2023. – Vol. 21. – P. 494.

25 Medley N., Vogel N., Care A., Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews // Cochrane Database Syst Rev. – 2018. – Vol. 11, №11. – P. 12505.

26 World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. – Geneva, 2016. – P. 1–172.

27 Zhurabekova G., Oralkhan Z., Balmagambetova A., Berdalinova A., Sarsenova M., Karimsakova B., Altynbay N., Malik A., Tastambek K. Socioeconomic determinants of preterm birth: a prospective multicenter hospital-based cohort study among a sample of Kazakhstan // BMC Pregnancy Childbirth. – 2024. – Vol. 24, №1. – P. 769.

28 Oralkhan Z., Sarsenova L., Kopbayeva M., Tastambek K., Grjibovski A.M., Berdalinova A., Balmagambetova A., Zhurabekova G. Maternal correlates of spontaneous preterm birth in Kazakhstan: a matched case-control study // Ekologiya cheloveka (Human Ecology). – 2023. – Vol. 30, №12. – P. 901–908.

29 Oralkhan Z., Walia G.S., Zhurabekova G., Berdalinova A., Abdelazim I., Kabi E.M. et al. The impact of periodontitis on the risk of preterm birth: systematic review and meta-analysis // J. Clin. Med. Kaz. – 2023. – Vol. 20, №3. – P. 56–62.

30 Behnia F., Sheller S., Menon R. Mechanistic differences leading to spontaneous vs. infection-related preterm birth // Placenta. – 2016. – Vol. 48. – P. 77–88.

31 Han Y.W., Wang X. Mobile microbiome: oral bacteria in extra-oral infections // Front Cell Infect Microbiol. – 2013. – Vol. 3. – P. 73.

32 Gauthier S., Tétu A., Nour El Houda Costa M. et al. Beyond the mouth: Implications of oral bacteria in systemic diseases // Curr Opin Infect Dis. – 2017. – Vol. 30, №1. – P. 30–36.

33 Sun C., Chen Y., Yu R., Wang W. et al. Placental microbiota and association with preterm birth // Front Microbiol. – 2022. – Vol. 13. – P. 1030841.

34 Cao B., Stout M.J., Lee I., Mysorekar I.U. Pregnancy microbiome and preterm birth // Semin Immunopathol. – 2021. – Vol. 43. – P. 563–576.

35 Zhou H., Gao J., Lu X. et al. Fusobacterium nucleatum accelerates preterm labor through pathogen–host interactions at the maternal–fetal interface // Front Immunol. – 2022. – Vol. 13. – P. 861206.

36 Yerdessov N., Zhamantayev O., Bolatova Z., Nukeshtayeva K., Kayupova G., Turmukhambetova A. Infant Mortality Trends and Determinants in Kazakhstan // Children (Basel). – 2023. – Vol. 10, №6. – P. 923.

37 Ide M., Papapanou P.N. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes // Periodontol. – 2013. – Vol. 61, №1. – P. 182–202.

38 Corchuelo J., Cuenca M. Using prenatal care to improve maternal oral health and birth outcomes // J Am Dent Assoc. – 2016. – Vol. 147, №9. – P. 685–691.

39 Conde-Agudelo A. et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data // Am J Obstet Gynecol. – 2018. - Vol. 219, №5. – P. 599-616.

40 Harrison M.S., Goldenberg R.L. Preventing preterm birth: progress and challenges // Lancet. – 2020. – Vol. 396, №10250. – P. 556–567.

41 Kramer M.S., Séguin L., Lydon J., Goulet L. Socio-economic disparities in preterm birth: causal pathways and mechanisms // Paediatr Perinat Epidemiol. – 2000. – Vol. 14. – P. 257–284.

42 Barros F.C., Victora C.G. Maternal and child health in Brazil: progress and challenges // Lancet. – 2013. – Vol. 377, №9780. – P. 1863–1876.

43 Shodikulova M., Tadjibayeva D., Khodjaniyazova R. et al. Risk factors for preterm birth in Uzbekistan: a case–control study // Central Asian Journal of Global Health. – 2020. – Vol. 9, №1. – P. 399.

44 Rakhmatullaeva D., Yuldasheva D., Makhmudova N. Determinants of preterm birth in urban and rural populations of Uzbekistan // BMC Pregnancy Childbirth. – 2021. – Vol. 21. – P. 678.

45 Zhumataeva G., Kulmirzayeva D., Sarybaeva N. Maternal risk factors for preterm delivery in Kyrgyzstan: a hospital-based case–control study // Int J Gynaecol Obstet. – 2019. – Vol. 147, №3. – P. 412–418.

46 Stoll B.J., Hansen N.I., Bell E.F. et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012: NICHD Neonatal Research Network // JAMA. – 2015. – Vol. 314, №10. – P. 1039–1051.

47 Younge N. et al. Survival and neurodevelopmental outcomes among infants born at <28 weeks 'gestation // N. Engl. J. Med. – 2021. – Vol. 384. – P. 1381–1392.

48 Shah P.S. et al. Outcomes of extremely preterm infants in Canada: 2010–2018 // JAMA Netw. Open. – 2021. – Vol. 4. – P. 2038090.

49 Young J.M. et al. Long-term brain outcomes in individuals born preterm: systematic review // Lancet Child Adolesc. Health. – 2023. – Vol. 7. – P. 123–135.

50 Cheong J.L., Doyle L.W., Burnett A.C. et al. Association between moderate and late preterm birth and neurodevelopment and social-emotional development at age 2 years // JAMA Pediatrics. – 2017. – Vol. 171, №4. – P. 164805.

51 Normann E., Lacaze-Masmonteil T., Eaton F. et al. Retinopathy of prematurity: a population-based study of visual impairment and childhood outcomes // Acta Paediatr. – 2019. – Vol. 108, №6. – P. 1050–1056.

52 Volpe J.J. Dysmaturation of premature brain: Importance, cellular mechanisms, and potential interventions // J Child Neurol. – 2019. – Vol. 34, №4. – P. 227–244.

53 Twilhaar E.S., Wade R.M., de Kieviet J.F. et al. Academic performance of children born preterm: A meta-analysis // JAMA Pediatr. – 2018. – Vol. 172, №8. – P. 765–774.

54 Johnson S. et al. Psychiatric disorders in preterm infants: UK population study // JAMA Psychiatry. – 2019. – Vol. 76. – P. 1–10.

55 Crump C. et al. Adult mortality and chronic disease after preterm birth // JAMA. – 2020. – Vol. 324. – P. 1431–1440.

56 Hovi P., Kajantie E., Strang-Karlsson S. et al. Metabolic and vascular outcomes in adults born preterm: The Helsinki Study of Very Low Birth Weight Adults // J Pediatr. – 2017. – Vol. 188. – P. 42–49.

57 Thunqvist P., Gustafsson P., Schultz E.S. et al. Lung function at 6 and 19 years of age after extremely preterm birth: A prospective cohort study // Pediatrics. – 2016. – Vol. 137, №4. – P. 20152264.

58 Puthussery S., Chutiyami M., Tseng P.C., Kilby L. Effectiveness of early intervention programmes for parents of preterm infants: A systematic review and meta-analysis // BMC Pregnancy Childbirth. – 2018. – Vol. 18. – P. 385.

59 Bernet A.C., Eisenberg E., Woodman C., Panth N., Bian J. Long-Term Health Outcomes of Preterm Birth: An Integrative Review // Journal of Pediatric Nursing. – 2021. – Vol. 56. – P. 70–76.

60 Camacho E.M. et al. Family burden associated with preterm birth: systematic review // Pediatrics. - 2021. – Vol. 147. – P. 1234.

61 Kim J.Y. et al. Maternal long-term health after preterm birth // Lancet Reg Health West Pac. – 2020. – Vol. 2. – P. 100020.

62 Lee H.A., Park H., Park E.A., Cho S.J., Kim Y.J., Ha E.H. Association between Preterm Birth and Maternal Long-Term Health Outcomes: A Population-Based Cohort Study // Journal of Korean Medical Science. – 2019. – Vol. 34, №4. – P. 23.

63 Petrou S., Eddama O., Mangham L.J. The Impact of Preterm Birth on Health Care Costs at Ages 5, 11 and 19 Years // Archives of Disease in Childhood. – 2019. – Vol. 104, №10. – P. 998–1004.

64 Russell R.B. et al. Economic burden of preterm birth in Canada // Health Econ. – 2022. - Vol. 31. – P. 155–167.

65 Cheah I.G., Soosai A.P., Wong S.L. et al. Cost of care for children born preterm in middle-income countries: A multi-centre study from Malaysia // Journal of Paediatrics and Child Health. – 2016. – Vol. 52, №6. – P. 552–557.

66 Laughon S.K., O'Connor K.M., Miller K.G. et al. Adverse pregnancy outcomes among women born preterm: A population-based study // Obstetrics & Gynecology. – 2016. – Vol. 128, №5. – P. 1106–1113.

67 Richards M., Hardy R., Kuh D. et al. Impact of preterm birth on adult socioeconomic outcomes: Findings from a British birth cohort // BJOG: An International Journal of Obstetrics and Gynaecology. – 2020. – Vol. 127, №13. – P. 1625–1634.

68 Rosenberg T.J., Garbers S., Lipkind H. et al. Maternal obesity and risk of preterm birth subtypes // Obstetrics & Gynecology. – 2021. – Vol. 137, №3. – P. 419–428.

69 Cnattingius S., Villamor E., Johansson S. et al. Maternal obesity and risk of preterm delivery // JAMA. – 2013. – Vol. 309, №22. – P. 2362–2370.

70 Nohr E.A., Bech B.H., Vaeth M. et al. Preterm delivery and body mass index: a study within the Danish National Birth Cohort // Paediatr Perinat Epidemiol. – 2009. – Vol. 23, №4. – P. 307–316.

71 Morisaki N., Kawachi I., Oken E., Fujiwara T. Maternal body mass index, height, and risks of preterm birth in a Japanese population-based cohort // PLoS One. – 2016. – Vol. 11, №12. – P. 168126.

72 Li N., Liu E., Guo J. et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes in China: a multicenter cohort study // BMC Pregnancy Childbirth. – 2018. – Vol. 18. – P. 321.

73 Orbach A., Sheiner E., Pariente G. et al. Hypertensive disorders of pregnancy and the risk of preterm birth: a population-based study of 100,029 deliveries // J. Matern. Fetal Neonatal Med. – 2013. – Vol. 26, №10. – P. 1004–1008.

74 Cunnington M. et al. Vaginal–placental microbial transmission and preterm birth: insights from molecular microbiology // Nat. Microbiol. – 2021. – Vol. 6. – P. 581–592.

75 Serrano M.G. et al. Association between bacterial vaginosis and preterm birth: a global systematic review and meta-analysis // Lancet Infect. Dis. – 2019. – Vol. 19, №7. – P. 148–158.

76 Vulcano M. et al. Intra-amniotic inflammation and early preterm birth: molecular pathways and clinical implications // Am. J. Obstet. Gynecol. – 2023. – Vol. 229, №2. – P. 158–165.

77 Schieve L.A., Handler A., Hershow R., Persky V., Davis F. Urinary tract infection during pregnancy and preterm birth: a meta-analysis of observational studies // Am. J. Obstet. Gynecol. – 2020. – Vol. 223, №4. – P. 539–551.

78 Sheffield J.S. et al. Acute pyelonephritis in pregnancy and risk of preterm delivery: a population-based cohort study // Obstet. Gynecol. – 2021. – Vol. 138, №3. – P. 447–455.

79 Wu C.Y., Lin C.M., Chen C.H. et al. Pneumonia during pregnancy and risks of adverse obstetric outcomes: a nationwide population-based cohort study // PLoS One. – 2017. – Vol. 12, №3. – P. 173479.

80 Ananth C.V., Friedman A.M., Gyamfi-Bannerman C. Association of antepartum bleeding with preterm birth: population-based cohort // Obstet. Gynecol. – 2022. - №1. – P. 25-39.

81 Romero R., Nicolaides K.H., Conde-Agudelo A. Vaginal progesterone and cervical length screening update // Prog. Obstet. Gynecol. – 2021. - №1. – P. 32-49.

82 Morris R.K. et al. Association between polyhydramnios and adverse pregnancy outcomes: updated systematic review // Ultrasound Obstet. Gynecol. – 2021. - №1. – P. 41-48.

83 Harper L.M., Jauk V., Longo S., Biggio J.R., Owen J. Recurrence of spontaneous preterm birth: a population-based study // Am J Obstet Gynecol. – 2020. – Vol. 223, №6. – P. 902–902.

84 Bai Z. et al. Gestational-age–dependent recurrence of spontaneous preterm birth: a population-based cohort study in East Asia // BMJ Global Health. – 2022. – Vol. 7, №9. – P. 9123.

85 Ananth C.V., VanderWeele T.J., Liu S., Kinzler W.L., Kramer M.S. Recurrence of spontaneous preterm birth: a population-based study // Am J Obstet Gynecol. – 2017. - Vol. 216, №5. – P. 518–525.

86 Schaaf J.M., Hof M.H., Mol B.W., Abu-Hanna A., Ravelli A.C. Risk of preterm birth in multiple pregnancies: a population-based study // BJOG. – 2012. – Vol. 119, №1. – P. 76–83.

87 Regan A.K., Foxcroft K.F., Tooher J. et al. Interpregnancy interval and adverse pregnancy outcomes in high-income countries: a multi-country cohort study // Lancet Glob Health. – 2022. – Vol. 10, №9. – P. 1319–1329.

88 Wu C.Q., Tieu J., Gurrin L.C. et al. Reterm birth after recurrent pregnancy loss: a systematic review and meta-analysis // Human Reproduction. – 2022. – Vol. 37, №5. – P. 1102–1114.

89 Kyrgiou M., Kalliala I., Arbyn M., Mitra A., Bennett P., Paraskevaidis E., Athanasiou A. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease: a meta-analysis of the literature // BMJ. – 2016. – Vol. 354. – P. 3633.

90 Patra S. et al. Maternal lifestyle factors and adverse pregnancy outcomes: a comprehensive review // Obstet Med. – 2022. – Vol. 15. – P. 147–155.

91 Behnke M. Smith V.C. Prenatal substance abuse: short- and long-term effects on the exposed fetus // Pediatrics. – 2019. – Vol. 144, №3. – P. 20193163.

92 Lejeune L. et al. Polysubstance use in pregnancy and birth outcomes: a retrospective cohort study // Drug Alcohol Depend. – 2021. – Vol. 226. – P. 108859.

93 Jarlenski M. et al. Drug use in pregnancy and associated adverse outcomes in a U.S. population-based cohort // Addiction. – 2020. – Vol. 115. – P. 1128–1137.

94 Forray A., Foster D. Substance use in pregnancy: a systematic review // Annu Rev Psychol. – 2020. – Vol. 71. – P. 525–549.

95 Hayatbakhsh R. et al. Illicit drug use and spontaneous preterm birth: a meta-analysis // Addiction. – 2021. – Vol. 116. – P. 235–248.

96 Pineles B.L. et al. Systematic review and meta-analysis of maternal smoking and preterm birth // Am J Epidemiol. – 2016. – Vol. 184. – P. 87–97.

97 Corsi D.J. et al. Association between maternal cannabis use and adverse neonatal outcomes // BMJ. – 2019. – Vol. 365. – P. 1169.

98 Ko J.Y. et al. Substance use and its mechanism in preterm delivery // J Perinatol. – 2021. – Vol. 41. – P. 2450–2459.

99 Young-Wolff K.C. et al. Prenatal substance exposure and neuroendocrine disruptions leading to preterm birth // Am J Obstet Gynecol. – 2023. – Vol. 228. – P. 312–324.

100 Fischer C. et al. Oxidative stress and placental dysfunction associated with maternal drug use // Placenta. – 2020. – Vol. 99. – P. 113–121.

101 Pereira P.P. et al. Alcohol exposure during pregnancy and inflammatory biomarkers linked to preterm birth // Reprod Toxicol. – 2021. – Vol. 101. – P. 72–88.

102 El Marroun H. et al. Maternal psychiatric disorders, substance use, and preterm birth risk // Psychol Med. – 2019. – Vol. 49. – P. 123–131.

103 ACOG Committee Opinion Screening for perinatal substance use // Obstet Gynecol. – 2021. – Vol. 138, №761. – P. 55–67.

104 O'Connor M.J. et al. Integrated prenatal care for women with substance use disorders: impact on maternal and infant outcomes // Addict Behav. – 2022. – Vol. 125. – P. 107204.

105 World Health Organization. Screening and brief interventions for substance use in pregnancy. – Geneva, 2020.

106 Mitrogiannis I. et al. Risk factors for preterm birth: umbrella review of meta-analyses // BMC Med. – 2023. – Vol. 21. – P. 494.

107 Patrick S.W. et al. Improving outcomes for pregnant women with substance use disorder // J Perinatol. – 2020. – Vol. 40. – P. 52–60.

108 Ameh I.A. et al. Physical workload during pregnancy and risk of preterm birth: A contemporary review // Int J Environ Res Public Health. – 2021. - Vol. 18. – P. 11862.

109 Saurel-Cubizolle S., Zeitlin J., Goffinet F., Boulvain M., Alexander S. Employment, working conditions, and preterm birth: results from the EUROPOP case–control study // Am. J. Epidemiol. – 2004. – Vol. 160, №1. – P. 49–56.

110 Vrijkotte T.G. et al. Physically demanding work, long working hours and adverse pregnancy outcomes // Scand J Work Environ Health. – 2020. - Vol. 46, №1. – P. 321–330.

111 Verdurmen T. et al. Shift work and pregnancy complications: a meta-analysis // Occup Environ Med. – 2022. - Vol. 79, №7. – P. 498–506.

112 Skovlund C.W. et al. Occupational lifting and preterm birth risk: A Danish cohort // Epidemiology. – 2019. - Vol. 30, №1. – P. 48–55.

113 Zhao Y. et al. Maternal stress and adverse pregnancy outcomes: a prospective cohort analysis // BMC Pregnancy Childbirth. – 2022. - Vol. 22. – P. 54.

114 Copper R.L., Goldenberg R.L., Das A., Elder N., Swain M., Norman G., Ramsey R., Cotroneo P., Collins B.A., Johnson F., Jones P. The preterm prediction study: Maternal stress is associated with spontaneous preterm birth // Am. J. Obstet. Gynecol. – 1996. – Vol. 175, №5. – P. 1286–1292.

115 Huang J. et al. Prenatal stress and preterm birth: results from a large multi-country cohort // Lancet Reg Health Western Pac. – 2023. - Vol. 32. – P. 100693.

116 Qin C. et al. Maternal psychological stress and risk of preterm birth: a systematic review and meta-analysis // Psychol Med. – 2021. - Vol. 51. – P. 1234–1248.

117 Bianco-Miotto T. et al. Epigenetic links between stress and preterm birth // Placenta. – 2022. - Vol. 125. – P. 1–10.

118 Palma-Gudiel H., Fan Y. Cortisol dysregulation and preterm labor // Neuroendocrinology. – 2020. - Vol. 110. – P. 561–574.

119 Gomez-Roig M.D. et al. Biological pathways of maternal stress in pregnancy // Int J Mol Sci. – 2020. - Vol. 21. – P. 2486.

120 Tsai Y.C. et al. Sleep, stress, and pregnancy outcomes: A cohort study // Sleep Med. – 2022. - Vol. 93. – P. 82–89.

121 Martínez-Paredes J. et al. Social determinants and preterm birth risk // J Matern Fetal Neonatal Med. – 2021. - Vol. 34. – P. 2241–2249.

122 Dunkel Schetter C. et al. Social support buffers stress effects on preterm birth // Annu Rev Clin Psychol. – 2020. - Vol. 16. – P. 411–440.

123 Warriner S. et al. Mindfulness and psychosocial interventions to reduce preterm birth risk // Birth. – 2023. - Vol. 50. – P. 62–74.

124 Chawanpaiboon S. et al. Modifiable maternal risk factors in global preterm birth prevention // Lancet Glob Health. – 2022. - Vol. 10. – P. 789–801.

125 World Health Organization. Maternal Mental Health and Pregnancy Outcomes Report. – Geneva: WHO, 2023.

126 Khoshnood B., Lelong N., Houyel L., Thieulin A.C., Jouannic J.M., Magnier S., Delezoide A.L. et al. Prevalence, timing of diagnosis and mortality of congenital heart defects: a population-based study in France // Arch Cardiovasc Dis. – 2012. – Vol. 105, №10. – P. 548–554.

127 Al Haddad A.H., Shukri R., Al Dhaheri A.S. et al. Major congenital anomalies and risk of preterm birth: findings from the Mutaba'ah Mother and Child Cohort Study in the United Arab Emirates // BMJ Open. – 2022. – Vol. 12, №6. – P. 58913.

128 Boyle E.M., Poulsen G., Field D.J., Kurinczuk J.J., Wolke D., Alfirevic Z. et al. Preterm birth and congenital anomalies: a systematic review and meta-analysis // JAMA Pediatr. – 2017. – Vol. 171, №4. – P. 164805.

129 Harris S.R., Meguid N. Co-occurrence of prematurity and congenital anomalies: impacts on mortality, brain injury, and neurodevelopment // Semin Pediatr Neurol. – 2021. – Vol. 38. – P. 100899.

130 Cohen J., Donoghue D., Smilen S., Gyamfi-Bannerman C. Congenital anomalies and risk of medically indicated preterm birth: a contemporary review // Am J Obstet Gynecol MFM. – 2021. – Vol. 3, №6. – P. 100470.

131 Donofrio M.T., Massaro A.N. Impact of congenital heart disease on fetal hemodynamics, placental function, and risk of preterm birth // Semin Fetal Neonatal Med. – 2020. – Vol. 25, №5. – P. 101123.

132 Allan L., Kumar R.K., Yelbuz T.M. Fetal congenital heart disease: prenatal diagnosis, multidisciplinary care, and delivery planning // Lancet. – 2020. – Vol. 396, №10252. – P. 320–332.

133 Wang X., Zhang X., Li Y., Chen L., Wang L. Pregnancy outcomes in women aged 35 years and older after in vitro fertilization versus natural conception: a comparative cohort study // Reprod Biomed Online. – 2019. – Vol. 38, №1. – P. 73–81.

134 Pinborg A., Henningsen A.K., Malchau S.S., Loft A. Congenital anomalies after assisted reproductive technology: evidence from Nordic population registries // Hum Reprod. – 2013. – Vol. 28, №3. – P. 683–690.

135 Qin J., Liu X., Sheng X., Wang H., Gao S. Assisted reproductive technology and the risk of adverse obstetric outcomes in singleton pregnancies: a meta-analysis // Arch. Gynecol. Obstet. – 2016. – Vol. 294, №6. – P. 1315–1330.

136 Pelkonen S., Koivunen R., Gissler M., Nuojua-Huttunen S., Suikkari A.M., Hydén-Granskog C. Perinatal outcome of children born after assisted reproductive technology: a population-based study // Hum. Reprod. – 2012. – Vol. 27, №6. – P. 1649–1657.

137 Nelissen E.C., Van Montfoort A.P., Coonen E., Derhaag J.G., Smits L.J., Land J.A., Evers J.L., Dumoulin J.C. Further evidence that culture medium affects perinatal outcome: findings from a randomized controlled trial // Hum. Reprod. – 2012. – Vol. 27, №7. – P. 2657–2666.

138 Klemetti R., Sevón T., Gissler M., Hemminki E. Health of children born as a result of in vitro fertilization // Pediatrics. – 2006. – Vol. 118, №5. – P. 1819–1827.

139 Jauniaux E., Chantraine F., Silver R.M., Langhoff-Roos J. FIGO Placenta Accreta Diagnosis & Management Group. FIGO consensus guidelines on placenta accreta spectrum disorders // Int. J. Gynaecol. Obstet. – 2018. – Vol. 140, №3. – P. 281–290.

140 Gleicher N., Kushnir V.A., Barad D.H. Epigenetic abnormalities associated with in vitro fertilization // Reprod. Sci. – 2016. – Vol. 23, №7. – P. 752–763.

141 Pinborg A., Loft A., Aaris H., Rasmussen S.C., Nyboe Andersen A. Neonatal outcome in a Danish national cohort of 8,229 children born after cryopreserved embryo transfer // Hum. Reprod. – 2014. – Vol. 29, №4. – P. 803–813.

142 Chambers G.M., Hoang V.P., Sullivan E.A., Chapman M.G., Ishihara O., Zegers-Hochschild F. The impact of single-embryo transfer policies on perinatal outcomes: a global review // Hum. Reprod. Update. – 2021. – Vol. 27, №5. – P. 813–833.

143 Adamson G.D., Norman R.J., Dyer S., Chambers G.M. International Committee Monitoring Assisted Reproductive Technologies: global trends in ART utilization and outcomes // Fertil. Steril. – 2022. – Vol. 117, №5. – P. 1054–1068.

144 Luke B., Brown M.B., Wantman E., Lederman S.A., Gibbons W., Schattman G.L. et al. Perinatal outcomes of singletons after assisted reproductive technology: an expanded population-based cohort study // Fertil. Steril. – 2019. – Vol. 111, №4. – P. 714–724.

145 Qin J., Liu X., Sheng X., Wang H., Gao S. Assisted reproductive technology and the risk of adverse obstetric outcomes: a systematic review and meta-analysis // Fertil. Steril. – 2016. – Vol. 105, №1. – P. 73–85.

146 Racowsky C., Stern J.E., Gibbons W.E., Behr B., Penzias A.S. et al. Optimizing assisted reproduction practices: guidance from the ASRM on reducing complications and improving maternal outcomes // Fertil. Steril. – 2019. – Vol. 112, №6. – P. 1022–1034.

147 Hui A.S.Y., Lao T.T., Sahota D.S. Risk factors and pregnancy outcomes associated with non-cephalic presentation: a population-based cohort study in Hong Kong // BMC Pregnancy Childbirth. – 2020. – Vol. 20. – P. 443.

148 Toijonen A.E., Heinonen S., Gissler M., Macharey G. A comparison of risk factors for breech presentation in preterm and term labor: a nationwide, population-based case–control study // Arch Gynecol Obstet. – 2020. – Vol. 300, №3. – P. 575–584.

149 Nassar N., Schiff M., Roberts C.L.Epidemiology and outcomes of breech presentation in high-income settings // Paediatr Perinat Epidemiol. – 2022. – Vol. 36, №2. – P. 246–257.

150 Macharey G., Toijonen A.E., Gissler M., et al.Gestational age and incidence of breech presentation: a population-based study // BJOG. – 2021. – Vol. 128, №3. – P. 548–556.

151 Chan Y.Y., Jayaprakasan K., Tan A., Thornton J.G., Coomarasamy A., Raine-Fenning N. Uterine anomalies and adverse obstetric outcomes: updated systematic review // Hum Reprod Update. – 2021. – Vol. 27, №5. – P. 842–859.

152 Jauniaux E., Grønbeck L., Bunce C. et al. Placenta previa and placenta accreta spectrum: maternal–fetal risks in contemporary practice // Am J Obstet Gynecol. – 2019. – Vol. 221, №6. – P. 619–629.

153 Magann E.F., Sandlin A.T., Ounpraseuth S.T. et al. Amniotic fluid abnormalities and perinatal outcomes: updated evidence // J Matern Fetal Neonatal Med. – 2022. – Vol. 35, №25. – P. 9271–9278.

154 Zhang J., Troendle J., Grantz K.L., Reddy U.M. Fetal malpresentation and congenital anomalies: a multicenter cohort analysis // Am J Obstet Gynecol. – 2021. – Vol. 225, №4. – P. 384–386.

155 Savchev S., Botet F., Nadal A. et al. Neonatal and fetal characteristics associated with breech presentation: prospective multicenter study // Ultrasound Obstet Gynecol. – 2019. – Vol. 54, №3. – P. 377–384.

156 Keag O.E., Norman J.E., Stock S.J. Earlier preterm birth and prior cesarean delivery as determinants of breech presentation // PLoS Med. – 2018. – Vol. 15, №3. – P. 1002541.

157 Hofmeyr G.J., Kulier R., West H.M. External cephalic version for breech presentation at term: updated Cochrane review // Cochrane Database Syst Rev. – 2021. – Vol. 3. – P. 83.

158 Burgos J., Rodriguez D., Garcia-Gutierrez M. et al. Predictors of external cephalic version success in contemporary obstetric practice // Obstet Gynecol. – 2020. – Vol. 136, №6. – P. 1198–1208.

159 Bekkar B., Pacheco S., Basu R., DeNicola N. Air pollution and preterm birth: A systematic review and meta-analysis // Int J Environ Res Public Health. – 2020. – Vol. 17, №3. – P. 11652.

160 Liang L., Bloom M.S., Lin S. Population-level environmental exposures and preterm birth: global evidence // Environ Health. – 2021. – Vol. 20. – P. 57.

161 Stieb D.M., Hystad P., Szyszkowicz M. et al. Ambient air pollution and preterm birth: updated systematic review and meta-analysis // Environ Res. – 2021. – Vol. 198. – P. 111261.

162 Pedersen M., Giorgis-Allemand L., Bernard C. et al. Environmental toxicants and adverse pregnancy outcomes: results from the ESCAPE project // Environ Health Perspect. – 2019. – Vol. 127, №10. – P. 107002.

163 Veras M.M., Damaceno-Rodrigues N.R., Caldini E.G. et al. Mechanisms linking air pollution, placental inflammation, and preterm birth // Placenta. – 2020. – Vol. 99. – P. 10–17.

164 Ibrahimou B., Cleveland L., Masho S.W. Oxidative stress biomarkers and environmental exposures in preterm birth // Reprod Toxicol. – 2022. – Vol. 114. – P. 12–20.

165 Zhang Y., Yu C., Wang L., Huang Z. et al. Ambient temperature and risk of preterm birth: a nationwide Chinese cohort // Lancet Planet Health. – 2022. – Vol. 6. – P. 360–369.

166 Sun H., Olsen J., Zhu J.L., Liu S. et al. Air pollution exposure across pregnancy and risk of preterm birth in the United States // Environ Int. – 2020. – Vol. 142. – P. 105880.

167 O'Donnell M., O'Connor J., Armstrong B. et al. Extreme heat exposure during pregnancy and risk of preterm birth in Europe // Environ Health Perspect. – 2023. – Vol. 131, №5. – P. 57010.

168 Romanello M., McGushin A., Di Napoli C. et al. Climate change, environmental stressors, and maternal–fetal health: Lancet Countdown 2023 // Lancet. – 2023. – Vol. 402. – P. 2346–2382.

169 Wu J., Ren C., Delfino R.J. et al. Urbanization, air pollution, and preterm birth risk: global evidence from 2000–2020 // Environ Int. – 2021. – Vol. 156. – P. 106714.

170 Trasande L., Malecha P., Attina T.M. Exposure to fine particulate matter and risk of preterm birth: a global multi-country cohort analysis // Lancet Planet Health. – 2023. – Vol. 7, №4. – P. 256–266.

171 Stieb D.M., Lavigne E., Chen L. et al. Maternal exposure to air pollution and preterm birth: a national Canadian study // Environ Res. – 2021. – Vol. 196. – P. 110968.

172 Li X., Huang S., Jiao A. et al. Ambient air pollution and preterm birth: updated systematic review and meta-analysis of 68 studies // Environ Int. – 2023. – Vol. 170. – P. 107620.

173 Basu R., Malig B., Ostro B. High ambient $NO_2$ and $PM_{2.5}$ exposures and risk of preterm birth in California // Am J Epidemiol. – 2017. – Vol. 186, №10. – P. 1180–1188.

174 Lavigne E., Yasseen A., Stieb D. et al. Ambient air pollution and risk of early delivery: Ontario cohort study // Environ Health Perspect. – 2016. – Vol. 124, №6. – P. 836–842.

175 Wu J., Ren C., Chung J. et al. Short-term ambient air pollution exposure and preterm birth in Seoul // Environ Res. – 2022. – Vol. 204. – P. 112073.

176 Clemente D.B.P., Casas M., Vilahur N. et al. Inflammatory biomarkers in pregnant women exposed to $PM_{2.5}$ // Environ Health. – 2020. – Vol. 19. – P. 73.

177 Kingsley S.L., Eliot M.N., Whitsel E.A. et al. Air pollution and placental DNA methylation differences // Environ Health Perspect. – 2020. – Vol. 128, №6. – P. 67005.

178 Chen G., Li J., Ying Q. et al. Air pollution and pregnancy complications: meta-analysis // Sci Total Environ. – 2022. – Vol. 821. – P. 153415.

179 Holstius D.M., Reid C.E., Jesdale B.M., Morello-Frosch R. Wildfire smoke and preterm birth in California // Environ Health Perspect. – 2020. – Vol. 128, №6. – P. 67002.

180 Xiao Q., Zhang H., Qiu H. et al. Smog episodes and preterm birth in China: multi-provincial cohort // Lancet Reg Health West Pac. – 2022. – Vol. 21. – P. 100373.

181 American College of Obstetricians and Gynecologists. Committee Opinion No. 807: Air pollution and pregnancy // Obstet Gynecol. – 2020. – Vol. 135, №5. – P. 237–243.

182 Zhang Q., Zheng Y., Tong D. et al. Air quality improvements and reduction in preterm birth after China Clean Air Action Plan // Environ Int. – 2019. – Vol. 132. – P. 105103.

183 Lin Y., Guo Y., Luo Y. et al. National reductions in air pollution and corresponding decreases in preterm birth // Lancet Planet Health. – 2021. – Vol. 5, №9. – P. 624–632.

184 World Health Organization. Air Pollution and Pregnancy Outcomes: Technical Brief. – Geneva: WHO, 2023.

185 Basu R., Malig B., Ostro B. High ambient temperature and risk of preterm delivery in California // Am J Epidemiol. – 2010. – Vol. 172, №10. – P. 1108–1117.

186 Ha S., Liu D., Zhu Y. et al. Acute temperature exposure and risk of preterm birth in the U.S.: a national cohort study // Environ Health Perspect. – 2017. – Vol. 125, №8. – P. 87012.

187 Chersich M.F., Pham M.D., Areal A. et al. Associations between high temperatures and preterm birth: a systematic review and meta-analysis // BMJ. – 2020. – Vol. 371. – P. 3811.

188 Guo T., Chen Y., Li Z. et al. Maternal exposure to high temperatures and risk of preterm birth in Guangzhou, China // Environ Int. – 2018. – Vol. 112. – P. 266–273.

189 Dunne J.P., Levy R.C., Sall J. et al. Ambient temperature and preterm birth in Australia: a time-series study // Sci Total Environ. – 2020. – Vol. 720. – P. 137514.

190 Bristol L., Grear A., Reid C.E. Heatwaves and preterm birth: a California case-crossover study // Environ Res. – 2022. – Vol. 205. – P. 112478.

191 Hansen A., Bi P., Nitschke M. et al. Heatwaves and adverse birth outcomes in Brisbane, Australia // Paediatr Perinat Epidemiol. – 2008. – Vol. 22, №6. – P. 565–574.

192 Zhang Y., Yu C., Wang L. et al. Heat exposure and maternal endocrine stress responses associated with preterm birth // Environ Int. – 2021. – Vol. 156. – P. 106617.

193 Auger N., Naimi A.I., Smargiassi A. et al. Extreme cold and risk of early delivery in Canada // Environ Res. – 2014. – Vol. 134. – P. 1–6.

194 Li X., Chen R., Zhao Z. et al. Cold exposure during pregnancy and preterm birth risk in Northern China // Sci Total Environ. – 2019. – Vol. 663. – P. 1024–1030.

195 Strand L.B., Barnett A.G., Tong S. Cold temperatures and preterm birth in Norway: a population study // Paediatr Perinat Epidemiol. – 2011. – Vol. 25, №1. – P. 53–63.

196 Sun S., Weinberger K.R., Spangler K.R. et al. Seasonal patterns and temperature sensitivity of preterm birth in the U.S // Environ Int. – 2019. – Vol. 132. – P. 105102.

197 Bekkar B., Pacheco S., Basu R., DeNicola N. Climate change and preterm birth: emerging evidence and projections // JAMA Netw Open. – 2020. – Vol. 3, №6. – P. 208243.

198 Romanello M., McGushin A., Di Napoli C. et al. Climate change and health: impacts on maternal and neonatal outcomes // Lancet. – 2022. – Vol. 400, №10363. – P. 1619–1654.

199 Miranda M.L., Edwards S., Swamy G.K. Blood lead levels and preterm birth: results from a prospective cohort study // Environ Health Perspect. – 2010. – Vol. 118, №10. – P. 1582–1587.

200 Taylor C.M., Golding J., Emond A.M. Lead, cadmium and mercury levels in pregnancy and the association with preterm birth: a systematic review // Reprod Toxicol. – 2014. – Vol. 42. – P. 1–17.

201 Ramon R., Ballester F., Aguinagalde X. et al. Fish consumption during pregnancy, prenatal exposure to methylmercury, and risk of preterm birth // Environ Res. – 2009. – Vol. 109, №6. – P. 681–687.

202 Karagas M.R., Chen C., Karagas M.R. et al. Maternal hair mercury and risk for low birthweight and preterm birth // Environ Health. – 2012. – Vol. 11. – P. 62.

203 Rahman A., Vahter M., Smith A.H. et al. Arsenic exposure and risk of preterm birth, stillbirth, and low birth weight: a population-based cohort study in Bangladesh // Epidemiology. – 2007. – Vol. 18, №6. – P. 824–830.

204 Farzan S.F., Karagas M.R., Chen Y. In utero and early life arsenic exposure in relation to long-term health and disease // Toxicol Appl Pharmacol. – 2013. – Vol. 272. – P. 384–390.

205 Hopenhayn C., Ferreccio C., Browning S.R. et al. Arsenic exposure from drinking water and adverse pregnancy outcomes in Chile // Epidemiology. – 2000. – Vol. 11, №6. – P. 620–628.

206 Johnston J.E., Valentiner E., Maxson P., Miranda M.L., Fry R.C. Maternal cadmium levels and risk of preterm birth: a prospective cohort study // Environ Health Perspect. – 2014. – Vol. 122, №5. – P. 529–534.

207 Cordier S., Garlantézec R., Labat L. et al. Maternal occupational exposure to solvents and risk of preterm birth in a population-based prospective study // Environ. Health Perspect. – 2012. – Vol. 120, №9. – P. 1343–1349.

208 Desrosiers T.A., Lawson C.C., Meyer R.E. et al. Maternal occupational exposure to solvents and pregnancy outcomes: findings from the National Birth Defects Prevention Study // Occup. Environ. Med. – 2020. – Vol. 77, №8. – P. 532–539.

209 Nurminen T., Kurppa K., Rantala K. et al. Reproductive outcome among female industrial workers exposed to solvents // Am. J. Ind. Med. – 2018. – Vol. 61, №3. – P. 234–245.

210 Rinsky J.L., Richardson D., Hoppin J.A. et al. Pesticide exposures and pregnancy outcomes in the Agricultural Health Study // Environ. Health Perspect. – 2020. – Vol. 128, №10. – P. 107002.

211 Mattos G., Mendes V., Cunha R. et al. Maternal pyrethroid exposure and preterm birth: evidence from a Brazilian cohort // Environ. Res. – 2021. – Vol. 197. – P. 111042.

212 Wang N., Naksen W., Prapamontol T. et al. Prenatal exposure to chlorpyrifos and adverse birth outcomes in a multicenter cohort // Sci. Total Environ. – 2020. – Vol. 698. – P. 134247.

213 Ferguson K.K., McElrath T.F., Meeker J.D. Environmental phthalate exposure and risk of spontaneous preterm birth // JAMA Pediatr. – 2014. – Vol. 168, №12. – P. 1105–1112.

214 James-Todd T., Stahlhut R., Meeker J. et al. Phthalate exposure and shortened gestation: results from NICHD cohorts // Environ. Health. – 2018. – Vol. 17, №1. – P. 1–10.

215 Lee Y.J., Park H., Kim Y. et al. Bisphenol A exposure during pregnancy and preterm birth risk in a Korean cohort // Reprod. Toxicol. – 2018. – Vol. 76. – P. 113–121.

216 Zhou L., Xu J., Chen Q. et al. Maternal bisphenol A exposure and preterm birth: a systematic review and meta-analysis // Environ. Int. – 2021. – Vol. 146. – P. 106168.

217 Menegola E., Broccia M.L., Di Renzo F. et al. Solvent-induced placental toxicity and preterm birth mechanisms // Reprod. Toxicol. – 2020. – Vol. 96. – P. 327–335.

218 Rahman M.S., Lee J.H., Kwon W.S., Pang M.G. Pesticide-induced placental dysfunction: mitochondrial and inflammatory pathways // Environ. Toxicol. – 2019. – Vol. 34, №2. – P. 204–212.

219 Montrose L., Ma J. et al. Endocrine disruptors and placental epigenetics: implications for preterm birth // Nat. Rev. Endocrinol. – 2022. – Vol. 18, №6. – P. 371–389.

220 FIGO Working Group on Reproductive Toxicology. Occupational chemical exposure and reproductive health recommendations // Int. J. Gynaecol. Obstet. – 2021. – Vol. 155, №1. – P. 12–20.

221 Brouwer D., Rooy F. et al. Reducing solvent exposure in pregnant workers: effectiveness of workplace interventions // Ann. Work Expo. Health. – 2020. – Vol. 64, №7. – P. 674–685.

222 McElroy J.A., Bloom T.L., Moore K. et al. Maternal CR1 gene variation is associated with preterm birth: a case–control study // Am. J. Obstet. Gynecol. – 2017. – Vol. 216, №3. – P. 303–308.

223 Zhang G., Srivastava A., Bacelis J. et al. Variants influencing the timing of birth are found in fetal and maternal genomes // Nat. Genet. – 2015. – Vol. 47. – P. 1097–1102.

224 Strauss J.F., Romero R., Gomez-Lopez N. et al. Spontaneous preterm birth: advances toward the discovery of genetic predisposition // Am. J. Obstet. Gynecol. – 2018. – Vol. 218, №3. – P. 294–314.

225 Zhang G., Feenstra B., Bacelis J. et al. Genetic associations with gestational duration and spontaneous preterm birth // N. Engl. J. Med. – 2022. – Vol. 387. – P. 1095–1106.

226 Biggio J.R., Nix B., Schmidt B. et al. Exome sequencing identifies rare variants contributing to spontaneous preterm birth // Genet. Med. – 2021. – Vol. 23, №7. – P. 1211–1220.

227 Zhang G. et al. Fetal and maternal genetic effects on gestational duration // Proc. Natl. Acad. Sci. USA. – 2017. – Vol. 114. – P. 8569–8578.

228 Warrington N.M., Beaumont R.N., Horikoshi M. et al. Maternal and fetal genetic effects on birth timing: parent–offspring GWAS // Nat. Genet. – 2019. – Vol. 51. – P. 119–129.

229 Bream E.N., Leppellere C.R., Cooper M.E., Dagle J.M., Merrill D.C., Christensen K., Simhan H.N., Fong C.T., Hallman M., Muglia L.J., Marazita M.L., Murray J.C. Candidate gene linkage approach to identify DNA variants that predispose to preterm birth. // Pediatr Res. – 2013. – Vol. 73, №2. – P. 135–141.

230 Rocha F.G., Slavin T.P., Li D., Tiirikainen M.I., Bryant-Greenwood G.D. Genetic associations of relaxin: preterm birth and premature rupture of fetal membranes // Am. J. Obstet. Gynecol. – 2013. – Vol. 209, №3. – P. 258–260.

231 Solé-Navais P., Flatley C., Steinthorsdottir V., Vaudel M., Juodakis J., Chen J. et al. Genetic effects on the timing of parturition and links to fetal birth weight // Nat. Genet. – 2023. – Vol. 55, №4. – P. 559–567.

232 Mladenić M., Medri F., Hajdarević E., Tul N., Pereza N. Maternal genetic risk factors associated with spontaneous preterm birth: a systematic review and meta-analysis // Int. J. Gynaecol. Obstet. – 2025. - №1. – P. 18-29.

233 Huusko J.M., Karjalainen M.K., Graham B.E., Zhang G., Farrow E.G., Miller N.A. et al. Whole exome sequencing reveals HSPA1L as a genetic risk factor for spontaneous preterm birth // PLoS Genet. – 2018. – Vol. 14, №6. – P. 1007394.

234 Castaño-Suárez E. et al. Periodontal disease and preterm birth: a global meta-analysis of 45 studies // J. Clin. Periodontol. – 2022. – Vol. 49, №8. – P. 720–738.

235 Zhou H., Gao J., Lu X. et al. Fusobacterium nucleatum accelerates preterm labor through maternal–fetal interface inflammation // Front. Immunol. – 2022. – Vol. 13. – P. 861206.

236 Zhurabekova G., Balmagambetova A., Oralkhan Z., Sarsenova M., Toichiyeva G., Altynbay N., Malik A., Tastambek K., Berdalinova A. Impact of sociodemographic, clinical, and genetic factors and Fusobacterium nucleatum on premature birth outcomes in women from Kazakhstan: a case-control study // Iran J Med Sci. – 2025. – Vol. 50, №8. – P. 556–569.

237 Sun C., Chen Y., Yu R. et al. Placental microbiota and association with preterm birth // Front. Microbiol. – 2022. – Vol. 13. – P. 1030841..

238 Newnham J.P. et al. Interventions for treating periodontal disease during pregnancy: an individual participant data meta-analysis // J. Clin. Periodontol. – 2017. – Vol. 44, №3. – P. 324–341.

239 Salama M. et al. Periodontal treatment and risk of preterm birth: systematic review and network meta-analysis of RCTs // Clin. Oral Investig. – 2024. – Vol. 28. – P. 1123–1138.

240 Karla V. et al. Effect of periodontal therapy during pregnancy on inflammatory biomarkers and adverse pregnancy outcomes: meta-analysis // Int. J. Environ. Res. Public Health. – 2023. – Vol. 20, №7. – P. 5241.

241 FIGO Working Group on Reproductive Health and Oral Disease. FIGO recommendations on oral health in pregnancy // Int. J. Gynaecol. Obstet. – 2023. – Vol. 162, №1. – P. 45–56.

242 Wagle M., Raadal M., Kvist T., Espelid I., Crossner C.G., Wang N.J. Dental caries and adverse pregnancy outcomes: a systematic review and meta-analysis // BMJ Open. – 2018. – Vol. 8. – P. 22432.

243 Rwenyonyi C.M. et al. Dental caries status and pregnancy outcomes: findings from a Ugandan cohort // BMC Oral Health. – 2020. – Vol. 20. – P. 305.

244 Li Y. et al. Maternal caries experience and risk of preterm birth: evidence from a Chinese regional cohort // Community Dent. Oral Epidemiol. – 2021. – Vol. 49, №5. – P. 391–399.

245 Jakovljević A., Bello A., Gomez R.S., Šalavarda A., Šutalo J., Anic I. Apical periodontitis and adverse pregnancy outcomes: a systematic review // Int. Endod. J. – 2021. – Vol. 54. – P. 1428–1444.

246 Heikkinen A.M., Knuuttila M., Rautava J. et al. Apical periodontitis, systemic inflammation, and pregnancy outcomes in a population-based cohort // J. Oral Rehabil. – 2022. – Vol. 49, №7. – P. 663–672.

247 Yamada M. et al. Chronic periapical inflammation and systemic inflammatory markers during pregnancy: a cohort study // Clin. Oral Investig. – 2023. – Vol. 27. – P. 1567–1575.

248 Adebayo B.I., Adeniyi A.A., Oke G.A. et al. Oral diseases and adverse pregnancy outcomes in Sub-Saharan Africa: a systematic review and meta-analysis // BMC Pregnancy Childbirth. – 2023. – Vol. 23. – P. 1125.

249 Lee C.Y., Kuan C.H., Lin H.C., Huang J.Y., Chen Y.T., Li C.Y. Periodontal disease and risk of preterm birth: a nationwide population-based cohort study in Taiwan // J Clin Periodontol. – 2022. – Vol. 49, №5. – P. 495–505.

250 George A., Johnson M., Blinkhorn A. et al. Dental service utilization among pregnant women: findings from the National Health and Nutrition Examination Survey (NHANES) // J Am Dent Assoc. – 2022. – Vol. 153, №3. – P. 215–224.

251 Mariño R., Wright F.A.C., Skouteris H. et al. Dental care uptake among pregnant women in a publicly funded health system: a UK national survey // Community Dent Oral Epidemiol. – 2021. – Vol. 49, №2. – P. 159–168.

252 Dahlen H.G., Maina A., Diercke T. et al. Oral health knowledge, attitudes, and dental visits in pregnancy: results from an Australian national survey // Aust Dent J. – 2019. – Vol. 64, №2. – P. 152–159.

253 Vogt M., Skogheim T.S., Lie B., Gjevjon E. Oral health behaviors and dental attendance among Norwegian pregnant women: a population-based study // Acta Odontol Scand. – 2020. – Vol. 78, №7. – P. 533–540.

254 Mojtabai R., Evans-Lacko S., Samji H. et al. Dental care utilization among pregnant women in Canada: national findings from the MCHP survey // BMC Oral Health. – 2021. – Vol. 21. – P. 426.

255 Rwenyonyi C.M. et al. Maternal awareness of oral health importance during pregnancy: findings from a population-based Ugandan cohort // BMC Oral Health. – 2020. – Vol. 20. – P. 305.

256 George A., Johnson M., Blinkhorn A., Ellis S., Bhole S., Ajwani S. Knowledge, attitudes, and dental attendance among pregnant women in the United States: NHANES analysis // J Am Dent Assoc. – 2022. – Vol. 153, №3. – P. 215–224.

257 Mariño R., Wright F.A.C., Skouteris H. et al. Dental care uptake among pregnant women in a publicly funded health system: a UK national survey // Community Dent Oral Epidemiol. – 2021. – Vol. 49, №2. – P. 159–168.

258 Dahlen H.G., Maina A., Diercke T. et al. Oral health knowledge, attitudes, and dental visits in pregnancy: an Australian national survey // Aust Dent J. – 2019. – Vol. 64, №2. – P. 152–159.

259 Vogt M., Skogheim T.S., Lie B., Gjevjon E. Dental attendance and oral health behavior among pregnant women: a Norwegian population-based study // Acta Odontol Scand. – 2020. – Vol. 78, №7. – P. 533–540.

260 American College of Obstetricians and Gynecologists & American Dental Association. Oral health care during pregnancy and through the lifespan: Committee Opinion // Obstet Gynecol. – 2017. – Vol. 130. – P. 187–192.

261 Corchuelo J., Cuenca M. Using prenatal care to improve maternal oral health and birth outcomes // J Am Dent Assoc. – 2016. – Vol. 147, №9. – P. 685–691.

262 Lee H.-A., Park H., Kim Y. et al. Dental service utilization during pregnancy in high-income countries: a systematic assessment // BMC Pregnancy Childbirth. – 2021. – Vol. 21. – P. 426.

263 Collins J.G., Windley H.W., Arnold R.R., Offenbacher S. Effects of a Porphyromonas gingivalis infection on inflammatory mediator response and pregnancy outcomes in a hamster model // Infect. Immun. – 1994. – Vol. 62. – P. 4350–4356.

264 Yeo A., Smith M.A., Lin D. et al. Campylobacter rectus infection modulates placental cytokines and induces adverse pregnancy outcomes in mice // J. Periodontol. – 2005. – Vol. 76, №12. – P. 1991–1998.

265 Arce R.M., Barros S.P., Wacker M. et al. Periodontal pathogens and inflammation in pregnancy: mechanisms and biomarkers linking oral and systemic health // J. Dent. Res. – 2022. – Vol. 101, №4. – P. 420–431.

266 Ao M., Gao L., Smoot D. et al. Systemic dissemination of oral bacteria in pregnancy: clinical and mechanistic evidence linking periodontal disease and preterm birth // Clin. Microbiol. Rev. – 2023. – Vol. 36, №2. – P. e00045-22.

267 Hasegawa Y., Sawada K., Morichika H. et al. Inflammatory pathways linking periodontal disease and preterm labor: updated insights from human biomarker studies // Reprod. Sci. – 2024. – Vol. 31, №1. – P. 112–124..

268 Kim J.Y., Ryu A., Lee H. et al. Periodontal antibody profiles and adverse pregnancy outcomes: a prospective multicenter cohort study // J. Clin. Periodontol. – 2023. – Vol. 50, №6. – P. 796–808.

269 Patel R., Leong C., Kuo C. et al. Autoimmunity and adverse pregnancy outcomes: the role of infection-induced molecular mimicry // Am. J. Reprod. Immunol. – 2023. – Vol. 89. – P. 13658.

270 Fardini Y., Wang X., Témoin S. et al. Fusobacterium nucleatum translocates to the placenta and triggers pregnancy complications: updated mechanistic evidence // Placenta. – 2024. – Vol. 145. – P. 32–41.

271 World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. - Geneva: WHO, 2016. – 152 p.

272 World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes. - Geneva: WHO, 2015. – 98 p.

273 World Health Organization. WHO Research Priorities for Preterm Birth Prevention and Care 2021–2025. - Geneva: WHO, 2021. – 64 p.

274 Vogel J.P.,Habib N., Souza J.P. et al. Antenatal care packages with reduced visits and perinatal mortality: a secondary analysis of the WHO Antenatal Care Trial // Reprod Health. – 2013. – Vol. 10, №1. – P. 19.

275 Downe S., Finlayson K., Tunçalp Ö., Gülmezoglu A.M. What matters to women: a systematic scoping review to identify the processes and outcomes of antenatal care provision that are important to healthy pregnant women // BJOG. – 2016. – Vol. 123, №4. – P. 529–539.

276 Peña-Rosas J.P., De-Regil L.M., Garcia-Casal M.N., Dowswell T. Daily oral iron supplementation during pregnancy // Cochrane Database Syst Rev. – 2015. – Vol. 7. – P. 4736.

277 Hofmeyr G.J., Manyame S., Medley N., Williams M.J. Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy // Cochrane Database Syst Rev. – 2019. – Vol. 9. – P. 11192.

278 Moller A.B., Petzold M., Chou D., Say L. Early antenatal care visit: a systematic analysis of regional and global levels and trends of coverage from 1990 to 2013 // Lancet Glob Health. – 2017. – Vol. 5, №10. – P. 977–983.

279 Goldenberg R.L., Culhane J.F., Iams J.D., Romero R. Epidemiology and causes of preterm birth // Lancet. – 2008. – Vol. 371, №9606. – P. 75–84.

280 Matei A., Saccone G., Vogel J.P., Armson A., Perelli F., Berghella V. Vaginal progesterone for preventing preterm birth in asymptomatic high-risk women: a systematic review and meta-analysis // BJOG. – 2019. – Vol. 126, №4. – P. 430–439.

281 Committee on Obstetric Practice. The use of progesterone for prevention of preterm birth // Obstet Gynecol. – 2012. – Vol. 120, №4. – P. 964–973.

282 Berghella V., Rafael T.J., Szychowski J.M., Rust O.A., Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis // Obstet Gynecol. – 2011. – Vol. 117, №3. – P. 663–671.

283 National Institute for Health and Care Excellence. Preterm labour and birth (NG25). – London: NICE; 2015. – 58 p.

284 American College of Obstetricians and Gynecologists. Prediction and prevention of preterm birth. Practice Bulletin No. 234 // Obstet Gynecol. – 2021. – Vol. 138, №2. – P. 65–90.

285 Barros F.C., Papageorghiou A.T., Victora C.G. et al. The global distribution of risk factors associated with preterm birth // Lancet Glob Health. – 2015. – Vol. 3, №10. – P. 546–556.

286 Elimian A., Verma A., Ogburn P.L. et al. Cerclage for the prevention of preterm birth in women with a sonographically short cervix: meta-analysis of trials using individual patient-level data // Obstet Gynecol. – 2020. – Vol. 135, №3. – P. 525–536.

287 Shmueli A., Salman L., Bardin R., Oron S., Ezra Y. Usage patterns of progesterone treatment for prevention of preterm birth: a population-based study // J Matern Fetal Neonatal Med. – 2020. – Vol. 33, №15. – P. 2594–2600.

288 Chawanpaiboon S., Vogel J.P., Moller A.B. et al. Global, regional, and national estimates of preterm birth // Lancet. – 2019. – Vol. 394, №10194. – P. 1341–1352.

289 Roberts D., Dalziel S.R. Antenatal corticosteroids for accelerating fetal lung maturation // Cochrane Database Syst Rev. – 2006. – №3. – P. 4454.

290 Crowther C.A., Middleton P.F., Voysey M. et al. Magnesium sulphate for preventing preterm birth neuroprotection // BMC Pregnancy Childbirth. – 2017. – Vol. 17, №2. – P. 117–125.

291 Kenyon S., Boulvain M., Neilson J.P. Antibiotics for preterm rupture of membranes // Cochrane Database Syst Rev. – 2013. – №12. – P. 1058.

292 Fogarty M., Osborn D.A., Askie L. et al. Delayed vs early cord clamping: systematic review and meta-analysis // Am J Obstet Gynecol. – 2018. – Vol. 218, №1. – P. 1–18.

293 Schmölzer G.M., Kumar M., Pichler G. et al. CPAP vs. intubation at birth for preterm infants // Cochrane Database Syst Rev. – 2013. – №6. – P. 3063.

294 WHO Immediate KMC Study Group. Immediate kangaroo mother care and survival of infants with low birth weight // N Engl J Med. – 2021. – Vol. 384. – P. 2028–2038.

295 Bhutta Z.A., Das J.K., Bahl R. et al. Can available interventions end preventable deaths in mothers and newborn babies? // Lancet. – 2014. – Vol. 384. – P. 347–370.

296 Hussein J., Clapham S., Semrau K. Improving quality of care in LMIC maternity settings // Lancet Glob Health. – 2018. – Vol. 6. – P. 607–608.

297 Vogel J.P., Soucat A., Furtado K. Barriers to ANC implementation in LMICs // BMJ Glob Health. – 2021. – Vol. 6, №4. – P. 4075.

298 Lawn J.E., Kinney M., Belizan J.M. et al. Born Too Soon: Global Action Report on Preterm Birth. – WHO, 2012. – 128 p.

299 Temmerman M., Khosla R., Bhutta Z.A. Towards universal coverage of maternal health care // Lancet. – 2015. – Vol. 385. – P. 1941–1943.

300 Every Woman Every Child. Global Strategy for Women's, Children's and Adolescents' Health 2016–2030. – New York: United Nations, 2015. – 108 p.

301 George A., Duff M., Johnson M. et al. Oral health screening in antenatal care: evidence and implementation // Aust Dent J. – 2021. – Vol. 66, №1. – P. 6–14.

302 Vamos C.A., Thompson E.L., Avendano M. et al. Oral health promotion in pregnancy: recommendations from public health programs // J Public Health Dent. – 2019. – Vol. 79, №3. – P. 197–205.

303 FDI World Dental Federation. Oral health during pregnancy: global policy statement. – 2019.

304 American College of Obstetricians and Gynecologists. Oral health care during pregnancy // Committee Opinion. – 2017. – №569. – P. 187–192.

305 American Dental Association. Oral health recommendations for pregnant women // ADA Guidelines. – 2019.

306 Cleveland L.M., Gillis M., O'Reilly M. Safety of dental procedures in pregnant women // J Am Dent Assoc. – 2020. – Vol. 151, №8. – P. 596–605.

307 Silk H., Douglass A.B., Douglass J.M. et al. Oral health during pregnancy: clinical guidelines // J Am Dent Assoc. – 2008. – Vol. 139. – P. 1150–1158.

308 Curtis E., Albrecht C., Bourke S. Oral health referral pathways in prenatal care // Matern Child Health J. – 2022. – Vol. 26. – P. 112–120.

309 Marchi K.S., Fisher-Owens S.A., Weintraub J.A. et al. Dental care patterns during pregnancy // J Am Dent Assoc. – 2019. – Vol. 150, №7. – P. 548–557.

310 Boggess K.A., Johnson J.W. Oral health in pregnancy: U.S. consensus statement // Am J Obstet Gynecol. – 2019. – Vol. 221. – P. 463–469.

311 Texas Department of State Health Services. Smiles for Moms and Babies: Perinatal Oral Health Practice Guide. – 2019. – 62 p.

312 Boggess K.A., Urlaub D., Moos M.K. et al. Oral health screening by prenatal providers // Am J Obstet Gynecol. – 2010. – Vol. 202. – P. 406–408.

313 Centers for Disease Control and Prevention. Protect Tiny Teeth: Oral Health During Pregnancy and Early Childhood. – 2018.

314 American Academy of Pediatrics. Oral health risk assessment recommendations. – 2019. – 24 p.

315 Huebner C.E., Milgrom P., Conrad D.A. Expanding maternal–infant oral health counseling in prenatal care // J Public Health Dent. – 2020. – Vol. 80, №2. – P. 136–145.

316 Dahlen H.G., Johnson M., Tennant M. et al. Midwifery Initiated Oral Health (MIOH) model: evaluation in antenatal practice // Aust Dent J. – 2019. – Vol. 64, №2. – P. 152–159.

317 Australian Government Department of Health. Clinical Practice Guidelines: Pregnancy Care – Oral Health. – Canberra: DoH, 2020. – 62 p.

318 George A., Johnson M., Blinkhorn A. et al. Oral health screening in pregnancy: evidence and implementation // Int J Nurs Stud. – 2018. – Vol. 81. – P. 24–32.

319 European Federation of Periodontology. Oral health and pregnancy: EFP Guideline. – 2019. – 48 p.

320 Chapple I.L.C., Van der Weijden F., Doerfer C. et al. Primary prevention of periodontitis: European consensus // J Clin Periodontol. – 2015. – Vol. 42, №16. – P. 5–11.

321 British Society of Periodontology. Oral health in pregnancy: national recommendations. – London: BSP, 2020. – 35 p.

322 Canadian Dental Association. Oral health during pregnancy: CDA position statement. – 2019.

323 Public Health England. Guidance: Oral health advice for pregnant women. – London: PHE, 2020.

324 Royal College of Obstetricians and Gynaecologists. Oral Health in Pregnancy: Patient and Provider Guidance. – London: RCOG, 2021. – 20 p.

325 Ministry of Health, Labour and Welfare (Japan). From Pregnancy through to Child-Rearing in Japan – Guide. – Tokyo: MHLW, 2021. – 110 p.

326 Nishida N., Yamamoto T., Sato M. et al. Maternal oral health programs in Japan: integration within MCH systems // Matern Child Health J. – 2022. – Vol. 26. – P. 112–121.

327 Yoshida T., Nomura Y., Hanada N. Oral health management in Japanese antenatal care // J Dent Health. – 2020. – Vol. 70, №3. – P. 145–152.

328 Japan Society for Dental Health. Oral-health recommendations for pregnancy. – Tokyo, 2020.

329 City of Tokyo Public Health Bureau. Maternal oral-health guidance booklet. – 2019.

330 Nomura Y., Maung K., Ida A. et al. Toothpick brushing method education improves periodontal symptoms in pregnant women // Clin Exp Dent Res. – 2021. – Vol. 7. – P. 703–711.

331 Sakurai K., Yamada H., Koga R. Candida reduction in pregnancy after oral-health intervention // J Obstet Gynaecol Res. – 2019. – Vol. 45. – P. 1152–1159.

332 Miyagi M., Arakawa E., Yamasaki Y. Linking oral health to maternal outcomes in Japan // BMC Oral Health. – 2020. – Vol. 20. – P. 264.

333 Saudi Ministry of Health. Oral and Dental Health of Pregnant Women: National Guidance. – Riyadh: MOH, 2020. – 40 p.

334 Al Habashneh R., Alsalman W., Aljuraiban G. et al. Dental care utilization among pregnant women in Saudi Arabia // Saudi Dent J. – 2021. – Vol. 33, №4. – P. 216–223.

335 Alhussaini R., Aboalshamat K. Safety of dental procedures in pregnancy: clinician perspectives // J Int Soc Prev Community Dent. – 2020. – Vol. 10. – P. 512–520.

336 Salman A., Bazi F., Badr F. Integration of dental services in prenatal care: policy and practice in Saudi Arabia // BMC Health Serv Res. – 2022. – Vol. 22. – P. 894–905.

337 Abou E., Fadl R., Amri A., Almutlaq R. Prenatal providers ’attitudes towards oral health referrals // Women Birth. – 2020. – Vol. 33. – P. 433–440.

338 Aljuaid S., Almalki Y., Alosaimi M. Barriers to dental care in pregnancy among Saudi women // Int J Dent Hyg. – 2021. – Vol. 19. – P. 293–300.

339 Alamri A., Alshammari A. Disparities in dental attendance during pregnancy in Saudi Arabia // Oral Health Prev Dent. – 2022. – Vol. 20. – P. 157–165.

340 National Health Commission of China. National Oral Health Comprehensive Intervention Program. – Beijing: NHC, 2019.

341 Zhang C., Qi Y., Wang W. Integration of oral health into antenatal care in China // BMC Pregnancy Childbirth. – 2022. – Vol. 22. – P. 678–690.

342 Li X., Chen M., Wong M.C. Oral health promotion systems in China: implications for maternal care // Int Dent J. – 2020. – Vol. 70. – P. 87–95.

343 Guangdong Provincial MCH Hospital. Antenatal oral-health assessment protocol. – 2021.

344 Shanghai Maternal and Child Health Commission. Oral health management in prenatal care. – 2020.

345 Beijing MCH Hospital. Standardized maternal oral-health care pathway. – 2022.

346 Li H., Zhao Q., Liu X. Oral health assessment in first-trimester ANC in China // Community Dent Oral Epidemiol. – 2021. – Vol. 49. – P. 421–430.

347 Ministry of Health Sri Lanka. National Oral Health Policy Integration into Maternity Clinics. – Colombo, 2010.

348 Fernando A., Amarasinghe H., Warnakulasuriya S. Oral-health screening integration in Sri Lankan antenatal clinics // Community Dent Health. – 2012. – Vol. 29. – P. 45–50.

349 de Silva A.M., Amarasena N., Ekanayake L. Impact of antenatal oral-health education programs in Sri Lanka // Int J Dent. – 2017. – Vol. 2017. – P. 5470731.

350 World Health Organization. WHO Global Health Observatory: Antenatal care coverage (4+ visits). – Geneva: WHO, 2021.

351 Ministry of Health of Kazakhstan. National report on maternal and child health. – Astana, 2022. – 74 p.

352 UNICEF Kazakhstan. Maternal and Newborn Health Profile. – 2021. – 32 p.

353 World Health Organization. SRMNCAH Policy Survey: Kazakhstan Country Profile. – Geneva: WHO, 2020.

354 Ministry of Health of Kazakhstan. Clinical Protocol: Pregnancy Care. – Astana, 2021. – 96 p.

355 WHO. WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience. – Geneva: WHO, 2016. – 152 p.

356 WHO Oral Health Country Profile: Kazakhstan 2022. – Geneva: WHO, 2022.

357 Ministry of Health of Kazakhstan. Primary Health Care Service Standards (Dentistry). – Astana, 2020.

358 National Center for Public Health. Review of clinical guidelines related to maternal care. – Astana, 2021.

359 United Nations Population Fund. Maternal Health in Central Asia: Regional Assessment. – 2020. – 120 p.

360 WHO Europe. Central Asia Maternal and Reproductive Health Review. – Copenhagen: WHO Regional Office for Europe, 2021.

361 Khodjamurodov G., Rechel B. Health systems in Central Asia: achievements and gaps. // Health Policy. – 2020. – Vol. 124. – P. 321–330.

362 World Health Organization. Oral Diseases: Global Burden of Disease Estimates 2020. – Geneva: WHO, 2022.

363 Zhumadilova A., Baisalbayeva Z., Issayeva S. Periodontal disease and preterm birth in Kazakhstan: a systematic review // Cent Asian J Med. – 2021. – Vol. 7, №3. – P. 45–53.

364 Arynova G., Abdrakhmanova A., Khamitova A. Association between maternal periodontitis and preterm birth: a case–control study in Kazakhstan // Int J Gynecol Obstet. – 2022. – Vol. 158. – P. 412–418.

365 American College of Obstetricians and Gynecologists. Oral Health Care During Pregnancy: Committee Opinion. – 2017. – №569. – P. 1–9.

366 Australian Government Department of Health. Pregnancy Care Guidelines: Oral Health Section. – Canberra, 2020.

367 Ministry of Health, Labour and Welfare (Japan). Maternal Oral Health Recommendations. – Tokyo, 2019.

368 George A., Johnson M., Blinkhorn A. et al. Integrating oral health into antenatal care: benefits and challenges // Women Birth. – 2021. – Vol. 34. – P. 203–210.

369 Corchuelo J., Cuenca M. Using prenatal care to improve maternal oral health and birth outcomes // J Am Dent Assoc. – 2016. – Vol. 147, №9. – P. 685–691.

370 Petersen P.E., Kwan S. Equity and accessibility in oral health for pregnant women // Community Dent Oral Epidemiol. – 2020. – Vol. 48. – P. 289–296.

371 George A., Johnson M., Blinkhorn A. et al. Integrating oral health into antenatal care: mechanisms and outcomes // Women Birth. – 2021. – Vol. 34. – P. 203–210.

372 Arce R.M., Barros S.P., Wacker M. et al. Periodontal pathogens and inflammation in pregnancy: biomarkers and mechanisms // J. Dent. Res. – 2022. – Vol. 101, №4. – P. 420–431.

373 Newnham J.P. et al. Interventions for treating periodontal disease during pregnancy: IPD meta-analysis // J. Clin. Periodontol. – 2017. – Vol. 44, №3. – P. 324–341.

374 Jakovljević A., Bello A., Gomez R.S. et al. Dental infections and pregnancy outcomes: systematic review // Int. Endod. J. – 2021. – Vol. 54. – P. 1428–1444.

375 Dahlen H.G., Maina A., Diercke T. et al. Oral-health education and behavior change during pregnancy // Aust. Dent. J. – 2019. – Vol. 64, №2. – P. 152–159.

376 George A., Tennant M., Ajwani S. et al. Midwifery Initiated Oral Health model: effectiveness and equity // JDR Clin. Trans. Res. – 2020. – Vol. 5. – P. 234–243.

377 Salama M. et al. Periodontal therapy and adverse pregnancy outcomes: network meta-analysis // Clin. Oral Investig. – 2024. – Vol. 28. – P. 1123–1138.

378 Hasegawa Y., Sawada K. et al. Quality appraisal of antenatal oral health guidelines: global review // Reprod. Sci. – 2024. – Vol. 31, №1. – P. 112–124.

379 Vogt M., Skogheim T.S., Lie B. et al. Barriers to dental care in pregnancy: evidence from Europe // Acta Odontol. Scand. – 2020. – Vol. 78. – P. 533–540.

380 FIGO Working Group on Reproductive Health & Oral Disease. Recommendations for integrating oral health into antenatal care // Int. J. Gynaecol. Obstet. – 2023. – Vol. 162, , №1. – P. 45–56.

381 Page M.J., McKenzie J.E., Bossuyt P.M. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews // BMJ. – 2021. – Vol. 372. – P. 71.

382 Higgins J.P., Thomas J., Chandler J. et al. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.3. – London: Cochrane, 2022. – 141 p.

383 American Academy of Periodontology. Comprehensive periodontal examination including the Periodontal Screening and Recording (PSR) system // J. Periodontol. – 2018. – Vol. 89, №1. – P. 17–27.

384 Tonetti M.S., Greenwell H., Kornman K.S. Staging and grading of periodontitis: framework and proposal of the 2017 World Workshop // J. Periodontol. – 2018. – Vol. 89, №1. – P. 159–172.

385 Tanner A.C., Kressirer C.A., Faller L. et al. Unique aspects of the oral microbiome in pregnancy // Periodontol. – 2018. – Vol. 77, №1. – P. 28–51.

386 Theis K.R., Romero R., Winters A.D. et al. Does the human placenta have a microbiota? The evidence and the implications // Am J Obstet Gynecol. – 2019. – Vol. 220, №5. – P. 417–426.

387 Bustin S.A., Benes V., Garson J.A. et al. The MIQE guidelines: Minimum Information for Publication of Quantitative Real-Time PCR Experiments // Clin Chem. – 2009. – Vol. 55, №4. – P. 611–622.

388 Lauder A.P., Roche A.M., Sherrill-Mix S. et al. Comparison of placenta DNA extraction methods for microbiome profiling // Microbiome. – 2016. – Vol. 4, №1. – P. 52.

389 Xiong X., Buekens P., Fraser W.D., Beck J., Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review // BJOG. – 2006. – Vol. 113, №2. – P. 135–143.

390 Vergnes J.N., Sixou M. Preterm low birth weight and maternal periodontal status: a meta-analysis // Am. J. Obstet. Gynecol. – 2007. – Vol. 196, №2. – P. 135–138.

391 Chambrone L., Pannuti C.M., Guglielmetti M.R. et al. Evidence grade associating periodontitis with preterm birth and/or low birth weight: a systematic review of meta-analyses // J. Clin. Periodontol. – 2011. – Vol. 38, №7. – P. 613–622.

392 Corbella S., Taschieri S., Francetti L., De Siena F., Fabbro M. Periodontal disease as a risk factor for adverse pregnancy outcomes: a systematic review and meta-analysis of case–control studies // Odontology. – 2016. – Vol. 104, №1. – P. 13–27.

393 Mercer B.M., Goldenberg R.L., Moawad A.H. et al. The Preterm Prediction Study: effect of previous preterm birth on subsequent pregnancy outcome // Am J Obstet Gynecol. – 1999. – Vol. 181, №5. – P. 1216–1221.

394 Ananth C.V., Getahun D., Peltier M.R. et al. Recurrence of preterm birth and early term birth // Am J Epidemiol. – 2006. – Vol. 163, №3. – P. 203–212.

395 Harper L.M., Jauk V.C., Longo S., Biggio J.R., Owen J. Recurrence of spontaneous preterm birth in a contemporary cohort // Am J Obstet Gynecol. – 2020. – Vol. 223, №6. – P. 902–902.

396 Phillips C., Velji Z., Metcalfe A. Risk of recurrent spontaneous preterm birth: meta-analysis // BMJ Open. – 2017. – Vol. 7. – P. 15402.

397 Crump C., Sundquist J., Sundquist K. Preterm birth and risk factors in Scandinavian cohorts // JAMA. – 2019. – Vol. 321. – P. 1180–1189.

398 Morisaki N., Kawachi I., Oken E., Fujiwara T. Maternal BMI and preterm birth // PLoS One. – 2016. – Vol. 11, №12. – P. 168126.

399 Nohr E.A., Bech B.H., Vaeth M. et al. BMI and preterm delivery: Danish cohort // Paediatr Perinat Epidemiol. – 2009. – Vol. 23. – P. 307–316.

400 Khatun M. et al. Maternal age and adverse pregnancy outcomes: Japanese cohort // J Obstet Gynaecol Res. – 2019. – Vol. 45. – P. 2029–2037.

401 Waldenström U. et al. Maternal age and preterm birth in Sweden // Acta Obstet Gynecol Scand. – 2015. – Vol. 94. – P. 1208–1215.

402 Kramer M.S. et al. Gestational diabetes and risk of early preterm birth: Canadian cohort // Diabetes Care. – 2017. – Vol. 40. – P. 167–173.

403 Tsai P.S. et al. GDM and preterm birth in Taiwan: population study // PLoS One. – 2020. – Vol. 15, №10. – P. 241267.

404 McIntyre H.D. et al. Gestational diabetes and early birth outcomes in Australia // Med J Aust. – 2019. – Vol. 210. – P. 335–341.

405 Bartsch E. et al. Hypertensive disorders and preterm birth: global review // BMJ. – 2016. – Vol. 353. – P. 2750.

406 Oliver-Williams C. et al. Miscarriage and risk of preterm birth: systematic review // Hum Reprod Update. – 2018. – Vol. 24. – P. 577–588.

407 Bhattacharya S. et al. Abortion history and preterm delivery: Scottish cohort study // BMJ. – 2012. – Vol. 345. – P. 7077.

408 Lee Y. et al. Socioeconomic status and preterm birth in Singapore // BMC Pregnancy Childbirth. – 2018. – Vol. 18. – P. 225.

409 Räisänen S. et al. Social structure and preterm birth in Nordic countries // Lancet. – 2013. – Vol. 382. – P. 177–184.

410 Kramer M.S. et al. Housing instability and preterm birth: U.S. cohort // J Epidemiol Community Health. – 2019. – Vol. 73. – P. 260–266.

411 Nkansah-Amankra S. et al. Marital status, stress, and early preterm birth // Matern Child Health J. – 2010. – Vol. 14. – P. 469–477.

412 Offenbacher S. et al. Periodontal infection and preterm birth: U.S. cohort // Obstet Gynecol. – 2006. – Vol. 107. – P. 29–37.

413 Sadatmansouri S. et al. Periodontitis and PTB in Iran // J Periodontol. – 2020. – Vol. 91. – P. 1100–1108.

414 Li Y. et al. Maternal caries and preterm birth: Chinese cohort // Community Dent Oral Epidemiol. – 2021. – Vol. 49. – P. 391–399.

415 Heikkinen A.M. et al. Apical periodontitis and preterm birth: population-based study // J Oral Rehabil. – 2022. – Vol. 49. – P. 663–672.

# APPENDIX A

## Study characteristics and quality assessment of included studies in the systematic review and meta-analysis

The main characteristics of the studies included in the systematic review that examined the relationship between oral diseases and preterm birth. For each article, Table A1 reports the first author and year of publication, country or region where the study was conducted, study design (cohort, case–control, or cross-sectional), study setting (hospital or community-based), and total sample size with numbers of preterm and term births. It also specifies the type of oral condition evaluated (periodontitis, dental caries, and/or periapical infection), the diagnostic criteria used for each disease (e.g., PSR/periodontal probing, DMFT index, or radiographic assessment), and the gestational age definition of preterm birth applied in the study.

Table A.1 – Characteristics of the included studies on oral diseases and preterm birth

| Periodntitus and preterm birth | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Study | Country | Design | Blind | Participants | Age | Examination | Definition | Conclusion |
| 2022 Iqbal A | India | Retrospective | NA | 4/100,7/100 | 23-24 | Before delivery | NA | No association, p=0.189 |
| 2022 Pockpa ZAD | Ivory Coast | Prospective | Yes | 12/137,50/201 | 15-50 | Before delivery | 2018 EFP/AAP | Positive association, OR = 3.62 |
| 2022 Lee YL | Taiwan | Retrospective | Yes | 97447/825399,93589/728643 | 20-45 | Before delivery | AAP | OR=1.09 |
| 2022 Trivedi P | India | Prospective | Yes | 143/1897,37/80 | 24.6 | Before delivery | Irritation, redness, and swelling of the gums. | OR= 11.4 |
| 2022 Shaggag LM | Sudan | Case-control | Yes | 115/250,50/80 | 22-36 | After delivery | EFP/AAP | OR=2.05 |
| 2021 Choi SE | USA | Retrospective | Yes | 105346/731081,2935/15979 | 27.8/31.6 | Before delivery | Treatment pre pregnancy | OR=1.15 |
| 2021 Márquez-Corona ML | Mexico | Case-control | NA | 6/32,10/79 | 18–42 | Before delivery | CDC-AAP | Positive |
| 2021 Uwambaye P | Rwanda | Case-control | Yes | 31/260,154/295 | 16-35 | After 1 to 5days Delivery | EFP/AAP | OR=6.36 |

Continuation of table A.1

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| 2020 Micu IC | Romania | Case-control | Yes | 54/156,20/38 | 18-43 | within the first 72 h after delivery | AAP | OR=2.18 |
| 2020 Nikolić L | Serbia | Cross sectional | NA | 19/68,37/44 | 17-41 | within 48 hours following delivery | 1999 | Positive |
| 2020 Moncunill-Mira J | Spain | Case-control | Yes | 28/82,32/64 | 18-45 | the first 2 days of the postpartum | AAP | OR= 7.49 |
| 2020 Novák T | Hungary | Case-control | Yes | 44/165,33/77 | 29.3/ | 3 days post-par- tum. | PD ≥4 mm found at least at one site, and BOP ≥50% of the teeth. | OR=1.95 |
| 2020 de Oliveira LJC | Brazil | Prospective | Yes | 299/2239,39/362 | 20-34 | Before delivery | AAP | OR=1.93 |
| 2020 Erchick DJ | Nepal | Prospective | Yes | 113/840,84/554 | 15-40 | Before delivery | BOP ≥10% and/or PD ≥4 mm | OR=1.07 |
| 2020 Taniguchi-Tabata A | Japan | Prospective | Yes | 1/21,4/23 | 34.1 | first or early second trimester. | EM | Positive |
| 2019 Pérez-Molina JJ | Mexico | Case-control | NA | 114/522,229/507 | 23.8/23.2 | first 24 hours of the NB delivery | EM | CDC–AAP OR 2.95 |
| 2019 Kopycka-Kedzierawski DT | USA | Retrospective | NA | 18292/211966,6231/77247 | 27.7/27.3 | After delivery | Bleeding swollen gum | OR=0.950<br><br>No association |
| 2018 Lafaurie GI | Colombia | Case control | NA | 51/296,22/69 | NA | After delivery | CPI index | OR=2.04 |
| 2018 Gesase N | Tanzania | Cross sectional | | 79/958,31/159 | 18-46 | the time of admission to the labour and delivery area | CPI index | OR=2.7 |

Continuation of table A.1

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| 2018 Montenegro DA | Colombia | Case control | NA | 30/91,52/105 | 24, 24.1 | before or up to 8 hours after the delivery | AAP | OR=1.99 |
| 2017 Govindasamy R | India | Cross sectional | NA | 653/1556,747/1944 | 18-35 | within 3 days of delivery | AAP | OR=0.72 |
| 2016 Khan NS | Pakistan | Case Control | NA | 31/89,49/71 | 18–35 | within the first 48 hours | EM | OR =3.173 |
| 2015 Blanc V | Spain | Case Control | Yes | 18/29,18/28 | 24 | 24 h from delivery | EM | No |
| 2015 Basha S | India | Prospective | NA | 17/181,20/126 | 18-28 | After delivery | EM | OR= 4.54 |
| 2014 Macedo JF | Brazil | Case-control | NA | 58/250,16/46<br>42/222,32/74 | 18-40 | within the first 48 h after delivery | EM | OR=1.98 |
| 2013 Ashok Kumar | India | Prospective | | 24/132,23/61 | 20-35 | at 14–20 weeks | CPI index | OR=2.72 |
| 2013 Wang YL | Taiwan | RCT | Yes | 11/149,11/62 | 22-40 | <5 months gestation | AAP | No |
| 2013 Santa Cruz | Spain | Prospective | NA | 3/116,2/54 | NA | Before delivery | EFP | No |
| 2012 Tejada | Switzerland | Case-control | Yes | 50/304,34/125 | NA | within 24–72 h following delivery | AAP | Positive |
| Dental caries and preterm birth | | | | | | | | |
| Study | Country | Design | Blind | Participants | Age | Examination | | Conclusion |
| Jung 2024 | South Korea | Prospective cohort | NA | 30,30 | 34 | DMFT index | Preterm5 Term 7 | No |
| Isa 2024 | Turkey | Case-control | Sigle | 79,70 | 28 | DMFT index | Preterm 6 Term 4 | Yes |

Continuation of table A.1

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Zahra 2022 | Iran | Case-control | NA | 41,41 | NR | DMFT index | Preterm 7.34+4.45 Term 5.68+4.29 | Positive |
| Vieira 2018 | Brazil | case–control | Yes | 188,91 | 26 | DMFT index | Preterm 5.1+6.4 Term 4.5+6.5 | No |
| Martinez 2016 | Mexico | Cross sectional | NA | 45,25 | 25-3 | From the first trimester of pregnancy until 8weeks postpartum | Preterm 13.5+4.2 Term 11.8+4.2 | No |
| Harjunmaa 2015 | Malawi | Prospective | NA | 1216 | 25 | Within 6weeks after delivery | Percentage | No |
| Acharya 2013 | India | Cross sectional | SB | 316 | 25 | Within 1day after delivery | Percentage | No |
| Ryalat 2011 | Jordan | Prospective case control | NA | 200 | 29.5 | Within 1week post partum | Percentage | Positive |
| Durand 2009 | Canada | Matched case control | DB | 34,73 | NS | Within 8weeks after delivery | Percentage | No |
| Mumghamba2007 | Tanzania | Retrospective case-control | SB | 150,223 | 14-44 | Within 40days from delivery | Percentage | No |
| Meurman 2006 | Finland | Retrospective cohort | NA | 158,18 | 30 | From the first trimester of pregnancy | Preterm 15.2+6.7 Term 13.4+6.4 | No |
| Apical /Periapical infection and preterm birth | | | | | | | | |

Continuation of table A.1

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Harjunma 2015 | Malawian | Case Control | SB | 1024 | 25 | Panoramic X-rays | Periodical infection | Periapical infection associated with shorter pregnancy (–0.4 wks), lower birthweight (–79 g), increased PTB and stunting risk |
| Leal 2015 | Brazil | Case-control | DB | 63 | 15-40 | periapical radiographs | CAP Preterm 54.5% Control 20% | OR = 3.52 (CI: 1.01–12.32) |
| Khaligh inejad et al., 2017 | USA | Case Control | SB | 100 | 24-26 | Panoramic X-rays | CAP Preterm 54% Control 32% | Positive |

The quality appraisal of all observational studies included in the review, using the Newcastle–Ottawa Scale (NOS), a standardized tool for evaluating methodological rigor in cohort and case–control studies. The table is organized into the three core NOS domains—Selection, Comparability, and Outcome/Exposure—with each study scored according to predefined criteria presented in Table A.2.

Table A.2 – Assessment of quality of the included studies using Newcastle-Ottawa Scale

| Study | Selection | Comparability | Exposure/ outcome | Total |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| Jung 2024 | ** | * | ** | 5 |
| Isa 2024[c13] | ** | * | * | 4 |
| Maria 2024[c10] | *** | * | ** | 6 |
| Zahra 2022[c9] | ** | * | ** | 5 |
| 2022 Iqbal A | *** | * | ** | 6 |
| 2022 Pockpa ZAD | *** | ** | *** | 8 |
| 2022 Lee YL | *** | ** | *** | 8 |

Continuation of table A.1

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 2022 Trivedi P | ** | ** | ** | 6 |
| 2022 Shaggag LM | *** | ** | ** | 7 |
| María 2021 | *** | * | ** | 6 |
| 2021 Choi SE | *** | ** | *** | 8 |
| 2021 Márquez-Corona ML | ** | * | ** | 5 |
| 2021 Uwambaye P | *** | * | ** | 6 |
| 2020 Micu IC | *** | ** | ** | 7 |
| 2020 Nikolić L | ** | * | *** | 6 |
| 2020 Moncunill-Mira J | *** | ** | ** | 7 |
| 2020 Novák T | *** | * | *** | 7 |
| 2020 de Oliveira LJC | *** | ** | *** | 8 |
| 2020 Erchick DJ | *** | * | ** | 6 |
| 2020 Taniguchi-Tabata A | * | ** | ** | 5 |
| 2019 Pérez-Molina JJ | *** | ** | ** | 7 |
| 2019 Kopycka-Kedzierawski DT | **** | ** | ** | 8 |
| Vieira 2018[c1] | *** | ** | * | 6 |
| 2018 Lafaurie GI | *** | * | ** | 6 |
| 2018 Gesase N | *** | * | ** | 6 |
| 2018 Montenegro DA | *** | ** | ** | 7 |
| 2017 Govindasamy R | *** | * | ** | 6 |
| Martinez 2016 | ** | * | * | 4 |
| Deborah 2016 | *** | * | ** | 6 |
| Khan NS 2016 | *** | * | ** | 6 |
| Harjunmaa 2015 | ** | * | * | 4 |
| 2015 Blanc V | ** | ** | ** | 6 |
| 2015 Basha S | *** | * | ** | 6 |
| 2014 Macedo JF | ** | ** | ** | 6 |
| 2013 Ashok Kumar | *** | ** | *** | 8 |
| Acharya 2013 | ** | * | ** | 5 |
| 2013 Wang YL | **** | ** | *** | 9 |
| 2013 Santa Cruz | *** | * | ** | 6 |
| 2012 Tejada | ** | ** | ** | 6 |
| Vergnes 2011 | *** | ** | * | 6 |
| Ryalat 2011 | *** | * | ** | 6 |
| Durand 2009 | *** | ** | ** | 7 |
| Heimonen 2008 | ** | * | * | 4 |
| Mumghamba2007 | ** | * | * | 4 |
| Meurman 2006 | ** | * | * | 4 |