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The impact of periodontitis on the risk of preterm birth: Systematic review and meta-analysis

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Abstract

Background: Preterm birth (PTB) is one of the most prevalent and serious adverse pregnancy outcomes (APOs) and major health risk for pregnant individuals and their children during pregnancy and throughout their lifespan. Periodontitis has long been regarded as a silent pandemic which happens to favor the pregnant women due to the physical and hormonal changes during pregnancy. Understanding of the association underscores the importance of keeping oral diseases under check and control to predict and even reduce the risk. The aim is to evaluate the association between periodontitis during pregnancy and preterm birth.

Material and methods: A screening and analysis was conducted on studies with comparison data about periodontal infection diseases during pregnancy and preterm birth. The databases include Scopus, PubMed, Elibrary, local databases and the Cochrane library and were searched up to November 20, 2022. The selected studies were included in a random-effects meta-analysis after evaluation of the methodological quality. The summary odds ratios (ORs) with 95% confidence intervals (CI) were calculated with Review Manager software.

Results: The review finally included 29 studies involving 2606589 pregnant women. Compared with healthy oral status in pregnancy, periodontitis was associated with preterm birth [OR=1.81, CI=1.60 to 2.03; p<0.001; I2 = 95%].

Conclusion: Periodontitis as one of the important factors is associated with increased risks of preterm birth. It is important to put the disease under control before and during pregnancy to reduce the preterm birth outcome.

Key words: pregnancy, preterm birth (PTB), periodontitis

Introduction

Preterm birth is a serious medical condition and remains one of the most intransigent research problems in obstetrics and gynecology in the world. According to the statistics, there were 1 in 10 babies born preterm, of these, 80% were born in Asia and Africa [1]. In Kazakhstan, this figure was 8.8 % and increased to 15.2% in 2017 [2]. According to experts of the Statistics Committee of the Ministry of National Economy in the country, despite the fact that the overall infant mortality rate in the country has decreased, these figures are still disappointing. In the Atyrau, Almaty and Aktobe regions, infant mortality is still high. In one center of the country alone, about 350 children are treated annually. About 200 of them were born prematurely.

The sequelae of preterm birth for the children ranging from significant morbidity such as mental retardation, vision impairment and cerebral palsy, to

mortality of the offsprings [3]. In the long term, preterm birth increased risk for cardiovascular disease, diabetes and cancer as an adult [3,4]. For the mother, delivering preterm increases her risk of a subsequent preterm delivery [4].

To date, advances in maternal prenatal care, increased public awareness and progress has been made in identifying the factors that may be connected with prematurity, as well as ruling out certain treatments that have not been shown to be effective [5]. Infection and host inflammatory response has long been associated with adverse pregnancy outcomes, including PTB [6]. Periodontitis has long been regarded as a silent pandemic which happens to favor pregnant women due to the physical and hormonal changes. It reported that periodontitis occurs about 2 to 3 times more often than genitourinary tract infections [7]. The role of periodontitis as one of the causation of adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes, preterm delivery, low birth weight infants has been extensively evaluated from observational evidence [8]. Periodontitis is a preventable and treatable disease, and it is thus necessary to identify the most common and representative predisposing factors among pregnant women may have a contribution to update a prenatal and perinatal oral health care protocol. Thus a better understanding of the nature of this association will assist in treatment planning to reduce adverse pregnancy outcomes.

This review considers whether the maternal periodontitis as a potential risk factor for preterm birth while there have been more and more recent studies reported conflicting results.

Material and methods

The study was conducted according to PRISMA guidelines [9]. The research question was generated as whether there was a higher risk of preterm birth among periodontitis affected pregnant population compared to the one with healthy periodontium. The databases include Scopus, PubMed, Elibrary, local databases and the Cochrane library and were searched up to November 20, 2022. Medical Subject Headings (MeSH) terms and keywords set as "Periodontal disease OR Periodontitis" AND “pregnancy”. Two authors screened the titles and abstracts after searching the databases and involved studies for final evaluation. All of the full text available articles evaluating oral health status during pregnancy and maternal and infant outcomes that met the following inclusion criteria were scrutinized and selected: observational study; population included pregnant people; Oral health status were evaluated with periodontal examination; comparisons included pregnant women with periodontitis versus those without periodontitis or with controlled status; outcomes included preterm birth. Reviews, Meta analyses, case reports, case series and abstracts were excluded from the study.

The following data was extracted from the studies included: author with year of publication, design of the study, the number of participants included in the study, definition of the oral diseases including periodontitis. The characteristics of the included studies are described in Table 1. Newcastle–Ottawa Scale was used to assess quality of the studies (Table 2).

Statistical analysis

Review Manager 5.4 was used to analyze the data extracted from the included studies. The associations between oral diseases and preterm birth and low birth weight were assessed and measures of effect were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The heterogeneity between studies was assessed with I2 statistics. The analysis was considered significant when $P<0.05$.

Results

The search strategy resulted in 1487 potentially relevant citations. 1304 initially searched studies excluded from further analysis after screening the title and abstract. The PRISMA Flow Diagram (Figure 1) summarizes the process of literature search and selection of studies. After screening the titles and abstracts, we read 67 full-text papers and included 29 studies with comparable outcomes [10-38].

Among the 2606589 pregnant participants, 827223 of them with maternal periodontitis and 1779366 unaffected pregnant controls assessed the oral infection on preterm birth in this study, compared with pregnant women without periodontitis, the pregnant women with 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; $p<0.001$; I2=95%] (Figure 2). A funnel plot was plotted and egger’s test was conducted to assess the presence of potential publication bias (Figure 3). There was no potential publication bias found (Table 3).

Discussion

Periodontal disease and other oral health problems have been supposed to be a risk factor for preterm birth in many literatures [2,8]. This systematic review and meta-analysis focuses on the most common and severe oral disease namely periodontitis with one of the adverse pregnancy outcomes, preterm birth. Our result found maternal periodontitis during pregnancy is associated with preterm birth compared with periodontal healthy pregnancies. This finding suggests that the health care system should adopt effective strategies to keep oral diseases under check and control to predict and even reduce the risk of exhibiting pregnancy related adverse outcomes.

Although several previous systematic review and meta-analysis regards the periodontitis and adverse pregnancy outcomes reported positive correlation between periodontitis and preterm birth [8], all of the studies showed the need for updating evidence while the number of well-designed publications from observational to experimental studies on this topic have been increased along with time.

The present study was based on the last global and local data, with more observed outcomes. As our results, the 29 individual studies included in the present investigation, which can be considered conflicting, since several of them indicate that there is no association between two health conditions. Another findings of our data searching and screening the methodological quality and design of the original data showed that local or neighbor studies from Central Asia on the aspect of oral health and its relation to maternal and child health is scarce. Well-designed evidence with clear diagnostic criteria of diseases with consideration of confounding factors are needed for contributing to the international database, while regional, genetic, dietary, hygiene, and health care differences contribute to different risks.

In accordance with the previously published systematic reviews, Our meta-analysis also suggests that the periodontitis during the pregnancy is one of the risk factors for occurrence of the preterm birth while the disease is multifactorial in nature. The mechanisms underlying the association could be explained by the theory that set as the periodontal pathogens may trigger an inflammatory response leading to elevated inflammatory cytokines level which would influence the degradation of the extracellular matrix of the fetal membranes and cervix [6,7]. It also could be explained as the periodontal pathogens, such as Fusobacterium nucleatum, migrates to the fetal-placental

Table 1 Characteristics of the included studies

Study	Country	Design	Blind	Participants	Age	Examination	PD definition	Conclusion
				Control/case				
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
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 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
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 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	cwithin 24–72 h following delivery	AAP	Positive

NA means not available.
CAL clinical attachment loss, PD probing depth
CDC-AAP: absent: PD<3mm and CAL<2mm; mild: PD≥3mm or CAL≥2mm; moderate: two or more sites with PD ≥ 5mm and two or more sites with CAL≥2mm; and severe: four or more sites with PD≥5 mm and four or more sites with CAL≥2 mm.
EFP/AAP classification, interdental CAL at two non-adjacent teeth with buccal/oral CAL≥3 mm, with pocketing >3 mm
CPI index: Clinical attachment loss and probing depth □4 mm in one or more site
EM: least four teeth with one or more sites with a probing depth of ≥4 mm and with clinical attachment loss of ≥3 mm [41]

Table 2 Assessment of quality of the included studies using Newcastle-Ottawa Scale.

Study	Selection	Comparability	Exposure/ outcome	Total
2022 Iqbal A	***	*	**	6
2022 Pockpa ZAD	***	**	***	8
2022 Lee YL	***	**	***	8
2022 Trivedi P	**	**	**	6
2022 Shaggag LM	***	**	**	7
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
2018 Lafaurie GI	***	*	**	6
2018 Gesase N	***	*	**	6
2018 Montenegro DA	***	**	**	7
2017 Govindasamy R	***	*	**	6
2016 Khan NS	***	*	**	6
2015 Blanc V	**	**	**	6
2015 Basha S	***	*	**	6
2014 Macedo JF	**	**	**	6
2013 Ashok Kumar	***	**	***	8
2013 Wang YL	****	**	***	9
2013 Santa Cruz	***	*	**	6
2012 Tejada	**	**	**	6

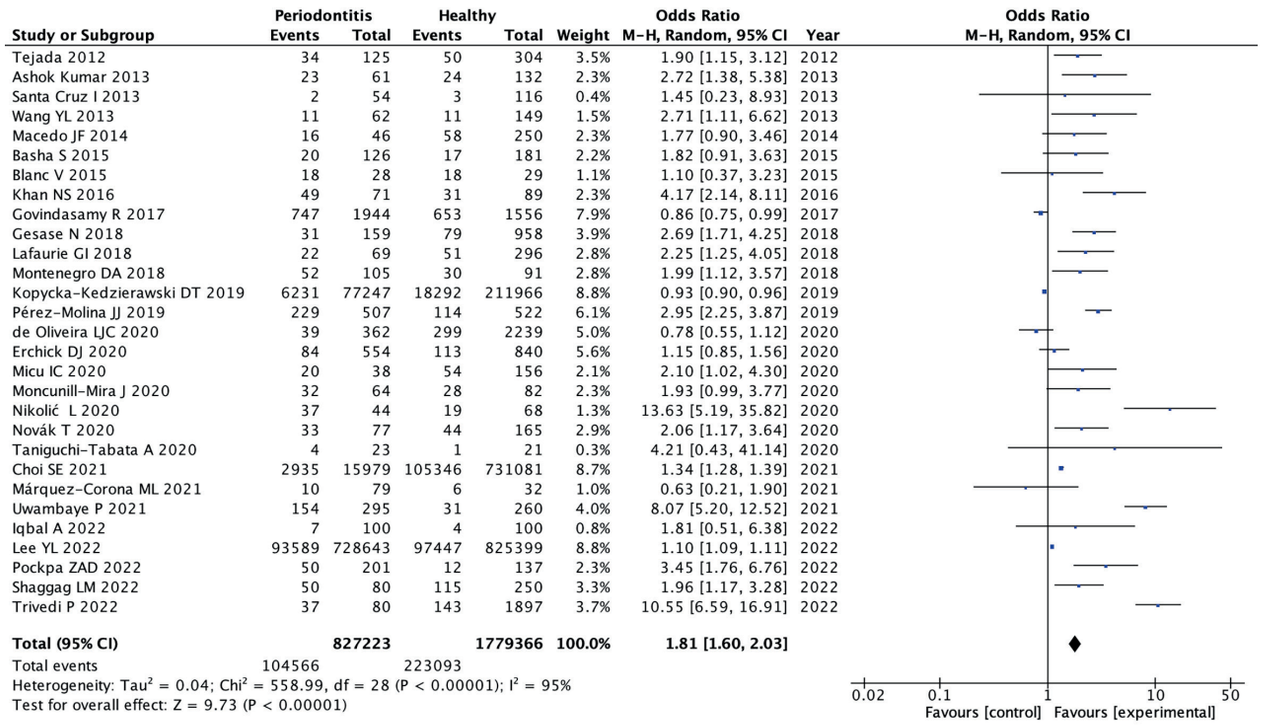

Figure 2 - Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the periodontitis and preterm birth.

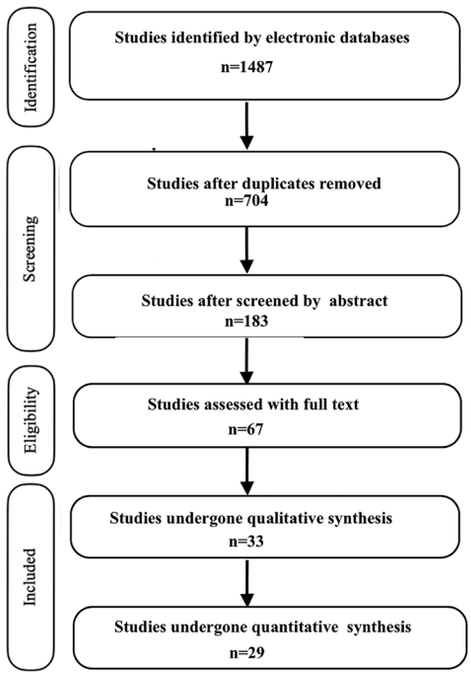

Figure 1 - Flow diagram of the study search and identification.

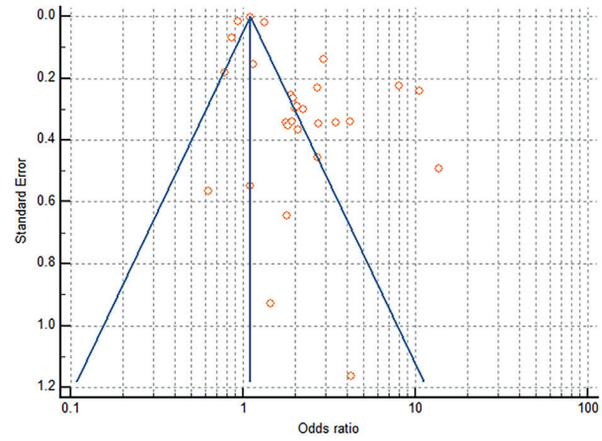

Figure 3 - Funnel plot for assessment of potential publication bias.

Table 3 Egger's test for potential publication bias in the included studies

Egger's test	
Intercept	2.2885
95% CI	0.6757 to 3.9013
Significance level	P = 0.0071

sections of the mother hematogenously, while these pathogens have been isolated from the placenta and amniotic fluid of preterm cases [39]. A most recent Israel study found that the high level of Gal-GalNAc, also known as Thomsen Friedenreich antigen during pregnancy mediates the placental colonization by Fusobacterium nucleatum [40].

Our study is limited by the inconsistent research design, as the includ studies regardless of the prospective and retrospective cohort and case control studies. Secondly, the unequal baseline of the sample in studies, such as geographic distribution, age, socio economic factors may also have influenced the heterogeneity of the studies, since most of the studies were carried out in the developed western countries. In addition, both health conditions share some major confounding factors, which may bias the estimates. In an attempt to minimize the possibility of publication bias, more databases were selected to search the original evidence. Furthermore, the diagnostic criteria for the periodontitis in the studies are difficult to standardize, while there are several diagnostic criteria presented in these studies and evaluated the association according to the definition used. In this sense, it is necessary to standardize criteria for determining periodontitis for pregnant women, which aims at greater methodological homogeneity between studies and a more consistent direction for the clinical practice of dental professionals. Further validation or substantiation about the association needs to collect more robust data.

Conclusion

Periodontitis during pregnancy must be considered as one of the important factors which is associated with increased risks of preterm birth. It is important to put the disease under control before and during pregnancy while it is preventable and treatable. It may be important to reduce the preterm birth outcome.

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