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ASSESSMENT OF ASSOCIATION BETWEEN MATERNAL PERIODONTITIS AND PRE-TERM LOW BIRTH WEIGHT INFANTS IN INDIAN POPULATION - A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Aim: To review the existing scientific literature and provide a novel evidence on association between maternal periodontitis and Pre-Term Low Birth Weight (PTLBW) infants in Indian scenario. **Methods:** Review was carried out in compliance with preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) criteria and registered in PROSPERO – CRD42023451699. Electronic databases were searched for studies having sufficient data on relation between maternal periodontitis and PTLBW infants and periodontal parameters like, plaque index (PI), probing depth (PD), clinical attachment loss (CAL), severity of bleeding index (BI) between cases (mothers with periodontitis) and controls (Mothers without periodontitis) was compared. Newcastle Ottawa Scale (NOS) was used to evaluate the quality of the included for dichotomous and continuous outcomes, the odds ratio and standardized mean difference (SDM) were employed as summary statistics, using the random effect model and p value <0.05 as statistically significant. **Results:** Fourteen studies after the evaluation of quantitative analysis showed that there was a significant association between cases and controls with regards to specific parameters like bleeding index, plaque index, probing pocket depth and CAL. Out of fourteen studies included in this eleven studies satisfied the eligibility requirements were included in the qualitative synthesis and qualified for meta-analysis. When compared to controls, cases had 0.89 times the chances (Odds ratio) of being linked with PTLBW newborns, but all of the evaluated periodontal parameters were substantially better in controls than in cases (p 0.05), according to this meta-analysis. The funnel plot used to analyze publication bias revealed a symmetric distribution and no evidence of systematic heterogeneity. **Conclusion:** Periodontitis in pregnant patients might be viewed as a significant risk factor for preterm birth and low birth weight. Preterm low birth weight birth is associated to maternal periodontitis in Indian population.

Keywords: Low Birth Weight, Periodontal Disease, Preterm Birth, Systematic Review.

INTRODUCTION

Periodontal disease is a multifactorial disease that affects the bone supporting the teeth and can result in tooth loss. Since periodontal disease exhibits few clinical symptoms, it often goes unrecognized until the illness is already advanced.[1]

Preterm low birth weight babies (PTLBW) and chronic obstructive pulmonary disorders (COPD) are one of the few examples in addition to CVS alterations and glycaemic levels leading to systemic health issues that might be impacted by periodontal inflammation and infection[2].

In the year 1995, low birth weight (LBW) is defined by the World Health Organization (WHO) as any live birth weighing less than 2500 gms[3] and very low birth weight (VLBW) as any live birth weighing less than 1500 gms[4] and occurring before 37 weeks

of gestation, which is still a serious public health issue.[5] For many years, there has been a link between periodontal and pregnancy health. Investigation is being done on the relationship between pregnant women's periodontal health and low birth weight (LBW) of the newborn.[6].

For the past few years, researchers have been interested in the link between maternal periodontitis and various pregnancy outcomes, including its existence and development.[7] Medical research also suggests that inflammatory processes in the fetus or placenta may alter pregnancy outcomes, the theory of which remains unchangeable.[8] An OR (Odd's ratio) of 1.82 from a meta-analysis of case-control studies demonstrates a substantial association between LBW and periodontitis in Italy.[9]

In the developing world, India accounts for over 40% of all LBW births.[10] Based on the information provided by studies, it is possible that one-third of all Indian newborns were born weighing less than 2.5 kilograms due to institutional births and small communities.[11] Infant mortality is greater in India's rural areas, which can be linked to a lack of resources for caring for preterm and low-birthweight babies.[12].

Numerous case-control studies conducted in India have investigated the link between periodontal disorders and unfavorable pregnancy outcomes. Almost all these studies have concluded that periodontitis of patients at the time of pregnancy considered to be a threat for PTLBW. However, there is no available literature of systematic review and meta-analysis. Hence, to assess this association and risk factor in the Indian population this review was conducted.

METHODS

Protocol development

The review was completed in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[13] and registered in PROSPERO with the registration ID of CRD42023451699.

Study design

P (Participants- Pregnant women),

E (exposure – Pregnant women having periodontitis),

C (Comparison – Pregnant women without periodontitis),

O (Outcome – to assess association between maternal periodontitis and infants with PTLBW with regards to various periodontal parameters).

Inclusion Criteria

a) Articles written in English were published.

b) Case control studies having sufficient data on association between maternal periodontitis and PTLBW infants.

c) Studies published between January 2000 – April 2024 and having relevant data on outcomes assessed like plaque index (PI), probing depth (PD), clinical attachment loss (CAL), severity of bleeding index (BI).

d) Articles showing the outcomes of study in terms of odds ratio (OR)

Exclusion Criteria

a) Any studies published before 2000 were excluded.

b) Articles in any other language except English was excluded.

c) Reviews, letter to the editor, abstracts, and editorials were excluded.

Data extraction

Following the descriptive study, information was gathered by 2 different authors and a Microsoft excel sheet with a pilot tested customized data collection form was made under the headings which were a part of final analysis: author(s), pregnancy duration, country of study, sample size, year of study, parameters assessed, and conclusion.

Search Strategy

Using the databases like PubMed-Medline, Scopus, Embase, Google Scholar, EBSCOhost and an extensive electronic search was conducted from January 2000 till April 2024. Cross references were explored for eligible studies, Greylist, Opengrey was investigated for grey literature.

A manual search of the oral surgery journals and the Journal of Periodontology, Journal of Indian Society of Periodontology, International Journal of Periodontology and Implantology, Journal of Periodontal and Implant Sciences, British Dental Journal, International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Periodontal Research, American Academy of Periodontology and the ADA journal was performed too.

Relevant key words and Medical Subject Heading (MeSH) terms were chosen and added along with Boolean operators like AND using the following keywords and their combinations: “Pregnancy” (MeSH term) AND “periodontitis” (MeSH term); “maternal periodontitis” (MeSH term) AND “plaque index” (MeSH term); “probing depth” (MeSH term) AND “clinical attachment level” (MeSH term) AND bleeding index severity (MeSH term); “gingivitis” (MeSH term) AND “gingival index” (MeSH term) AND “pre-term birth” AND “low birth weight” AND “prospective study” (MeSH term); “association” AND “case control study”.

Screening Process

Two authors carried out the search and screening in accordance with the defined methodology. The articles were chosen in two stages. Two reviewers looked over the titles and abstracts of each paper in phase one.

Articles that didn't meet the requirements for inclusion were disqualified. In step two, the same reviewers independently evaluated and vetted the chosen full articles. Any disagreements, if any, were settled through conversation.

A third reviewer was brought in to make the ultimate judgment when two reviewers could not agree upon something. All three authors came to agreement on the choice in the end. When more information was needed, the study's corresponding authors were contacted by email.

Quality assessment of included studies

Designed to assess bias depending on the selection of participants, comparison of groups in the cross sectional studies, exposure attained in case control studies and favourable outcomes in the cohort study.

Newcastle Ottawa Scale was used to evaluate the included studies' quality for observational studies, and a numerical score (NOS Score) was appropriately awarded.[15] It demonstrates to be a viable & reliable technique regarding non-randomized study quality evaluation, which is recommended by Cochrane Collaboration for quality assessment of non-randomized trial.

NOS employs nine-star grading system, with maximum of four selection points, including 2 and 3 points of comparability and evaluation of the outcome or exposure respectively. The effectiveness of an intervention was not being examined, hence the technique was judged appropriate for the evaluation of cross-sectional research.

The quality of the studies included was evaluated by 2 authors and in the event of a disagreement, a third author was contacted. A study is deemed as good quality with score of 7-9, moderate quality with a score of 4-6 and a score of 0- 3 would be deemed low-quality or extremely high risk of bias.

Assessment of heterogeneity

With use of the Cochran's test and I2 statistics, the heterogeneity was evaluated [16] A rough guide to the interpretation of I^2 is-

(1) Heterogeneity not important (0 to 40%)

(2) Moderate heterogeneity (30% to 60%)

(3) Substantial heterogeneity (50% to 90%)

(4) Considerable heterogeneity (75% to 100%)

Investigation of publication bias

Begg's funnel plot was used to evaluate the bias in publications.[17] Asymmetry might reflect a link in trial size and effect magnitude, it also indicates publication bias and other sample size-related biases.

Statistical analysis

The odds ratio (OR's) for the dichotomous outcome and standardized mean difference (SDM) with 95% CI was calculated for the continuous outcomes [14] through random effects model using the RevMan 5.3 and keeping the significance level at $p<0.05$

RESULTS

Study Selection

After duplicates were eliminated, the reference lists for the studies that were included were checked. 116 of the studies were left out. Following this, full text articles were evaluated for eligibility; those that did not match the requirements for inclusion were eliminated.

The qualitative synthesis had fourteen studies that met the qualifying requirements. Of which, a meta-analysis covered eleven trials. An outline of how to identify, include, and exclude research. A flowchart of identification, inclusion and exclusion of studies is shown in Figure 1.

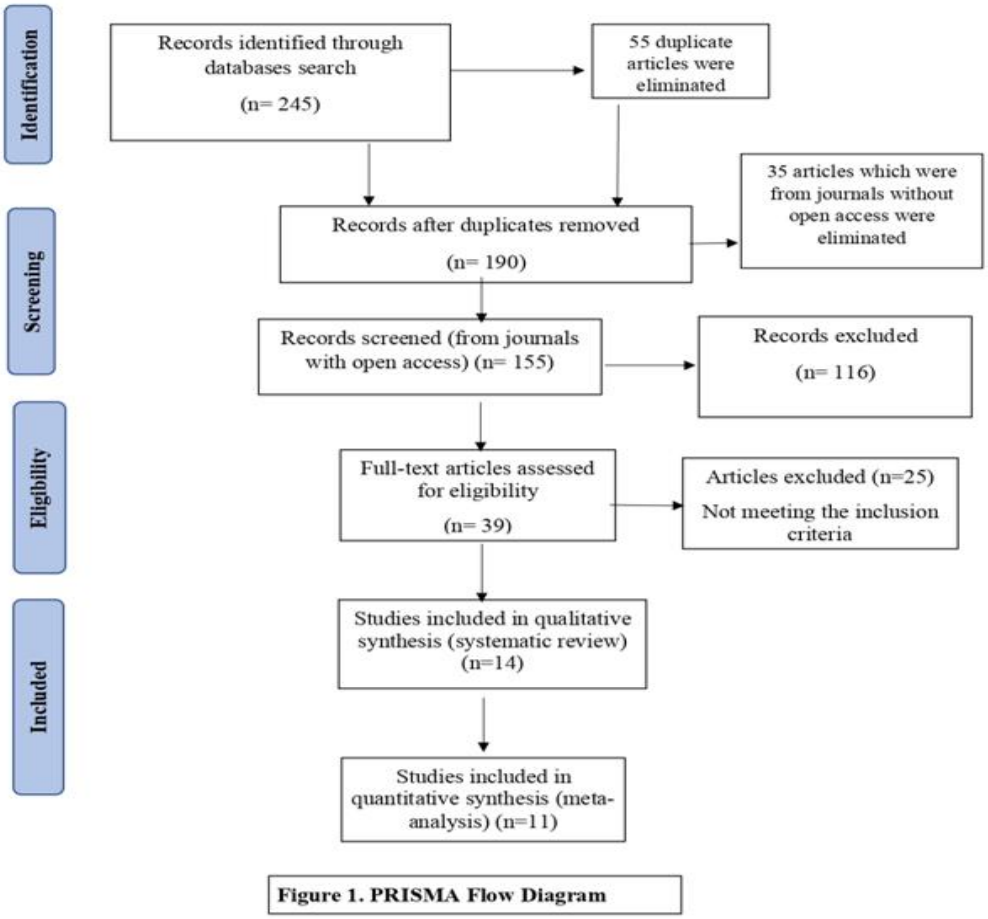

Figure 1. PRISMA Flow Diagram

Table 1: Showing descriptive characteristics of included studies

Author, years of study	Country	Study design	Sample size	Pregnancy duration	Parameters assessed	Conclusion
Mannem et al. 2011[19]	India	Case-control	104	Cases- preterm labour (infants <37 weeks. Controls- term labour (infants ≥37 weeks)	PI, BI	periodontal disease could be a risk factor for preterm labour
Chakki et al. 2012[20]	India	Case-control	62	primiparie mothers and mothers with full-term delivery (37 weeks or more)	PI, CPI	Periodontal disease was significantly related to preterm low birth weight
Jacob et al. 2014[21]	India	Case-control	340	Cases- women giving birth to babies weighing <2.5kgs Controls- women giving birth to babies weighing >2.5kgs	BOP, CAL, PD	Periodontitis represents a strong, independent, and clinically significant risk factor for LBW
Kumari et al. 2016[22]	India	Case-control	150	Cases -women delivering babies weighing <2.5 kg before 37 completed weeks of gestation and controls – women delivering babies weighing 2.5 kg at complete gestation	PD, BOP, CPITN scoring	severe periodontal disease (CPITN) was more prevalent in women with pre-term LBW babies
Sethi et al. 2016[23]	India	Case-control	91	Cases – infants delivered <37 weeks and < 2500 gms	PI, GI, PPD, CAL	association between maternal periodontal disease and the risk of

				Controls – infants delivered after 37 weeks with >2500 gms.		pre-term low birth weight infant was seen
Tellapragada et al.2016[24]	India	Case-control	790	Cases – infants delivered <37 weeks and < 2500 gms Controls – infants delivered after 37 weeks with >2500 gms.	CPI	There is a need to consider screening for potential periodontal infections during routine antenatal care
Keshava et al. 2017[25]	India	Case-control	60	Cases – infants delivered <37 weeks and < 2500 gms Controls – infants delivered after 37 weeks with >2500 gms.	PD	Strong and positive association was observed between maternal periodontitis and low birth weight infants
Lohana et al. 2017[26]	India	Case-control	300	20-24 weeks of gestation	PPD, CAL, OHI, PI.	Periodontal disease is a potential risk factor for preterm low birth weight babies of pregnant women
Priyanka et al. 2019[27]	India	Case-control	90	Cases- maternal women with periodontitis Control – maternal women without periodontitis	CAL, GI, PI	Maternal periodontitis is found to be associated with preterm and low birth weight deliveries. The severity of periodontitis is inversely related to gestational age at delivery and birth weight of infant.
Vidhale et al. 2020[28]	India	Case-control	90	Cases- patients having preterm delivery and low birth weight infants. Control- patients having full term delivery with normal birth weight infants	DI, PBI, CAL, PPD, GR.	significant relationship seen between maternal periodontal disease and preterm birth and low birth weight
Balaji et al. 2021[29]	India	Case-control	330	Cases- preterm labour (infants <37 weeks. Controls- term labour (infants ≥37 weeks)	PD, PI	Bidirectional association was observed between maternal periodontitis and low birth weight infants
Sinha et al. 2022[30]	India	Case-control	150	Cases – infants delivered <37 weeks and < 2500 gms Controls – infants delivered after 37 weeks with >2500 gms.	Russel periodontal index	periodontal disease in pregnant women may increase the risk of preterm delivery and low birth weight in infants
Vijay et al. 2022[31]	India	Case-control	100	Cases – pregnant mothers with CPI score 3 Controls - pregnant mother with CPI score 1 or 2	CPI, CAL	illiteracy of the mother plays a major role in causation of periodontal disease as well as to PTLBW
Anu et al. 2023[32]	India	Case-control	60	Cases- preterm birth and low birth weight babies Controls- normal term gestation and normal birth weight babies	CPI	Association between the preterm labour and birth type of babies with maternal periodontitis was seen. Maternal periodontitis are 56 times risk of preterm labour and low birth weight

Study Characteristics

List for elaborative features of each study that was included are shown in **Table 1.** Data was evaluated from fourteen studies[18-31] from an aggregate of 2717 participants. All the included studies were conducted in India and had case control study design.

Cases were the maternal mother with periodontitis while controls were maternal mother without periodontitis. The ideal definition of cases in included studies was mothers giving birth to babies before 37 gestational weeks and babies weighing <2.5 kgs while controls were mothers giving birth to babies after 37 gestational weeks and babies weighing >2.5 kgs. Various periodontal parameters assessed between cases and controls were BI, BOP, CAL, CPITN, GI, GR, OHI, PBI, PI and PD. Most of the included studies concluded that a strong and positive association was observed between maternal periodontitis and PTLBW and that periodontal disease was closely associated with PTLBW. Vijay et al.[30] concluded that illiteracy of the mother plays a major role in causation of periodontal disease as well as to PTLBW.

Periodontal Findings

Multiple periodontal variables were evaluated between cases and controls in all the included studies for their association between PTLBW. The comparison revealed a significant association between cases and controls with regards to specific parameters like bleeding index, plaque index, probing pocket depth and CAL. It was observed that severity of bleeding index was 1.19 times (SMD) more in cases. While cases had more plaque index 1.42 (SMD) and pocket depth 0.57 (SMD) compared to controls and observations were statistically significant ($p<0.05$). Clinical attachment loss was 2.42 (SMD) times more in cases. This qualitative data revealed a strong, positive and bi-directional association between maternal mothers with periodontitis and risk of PTLBW. Also, it was concluded by Tellapragada et al.2016[23] said that during standard prenatal care, it is important to think about screening for suspected periodontal infections.

Assessment of methodological Quality of included studies

Only two of eligible studies, [22] [28] received the highest possible Newcastle Ottawa score. Three studies[20,24,32] had the lowest score in comparability outcome and the lowest level of quality which estimated high risk of bias; all studies had a partial score in the exposure outcome, but only two studies[18,29] had the lowest score for exposure outcome having the lowest level; and only two studies[22,28] had highest score within selection criteria, was seen to have highest degree of quality having a predicted low risk bias low risk bias.

Author, year of publication	Selection (Max = 4)	Comparability (Max = 2)	Exposure (Max = 3)	Overall quality score (Max = 9)
Mannem et al. 2011[18]	**	**	*	5
Chakki et al. 2012[19]	**	**	**	6
Jacob et al. 2014[20]	***	*	**	6
Kumari et al. 2016[21]	**	**	***	7
Sethi et al. 2016[22]	****	**	***	9
Tellapragada et al.2016[23]	**	*	**	5
Keshava et al. 2017[24]	**	**	**	6
Lohana et al. 2017[25]	**	**	**	6
Priyanka et al. 2019[26]	***	**	**	7
Vidhale et al. 2020[27]	****	**	***	9
Balaji et al. 2021[28]	**	**	*	5
Sinha et al. 2022[29]	**	**	**	6
Vijay et al. 2022[30]	***	**	**	7
Anu et al. 2023[31]	**	*	**	5

Figure 2: Quality assessment of included studies through Newcastle Ottawa scale (NOS)

Synthesis of meta-analysis

Eleven studies[18,20-22,24,26-31] were involved in meta-analysis. Pooled odds ratio (OR's) was calculated as a summary measure for association between maternal periodontitis and PTLBW as shown in figure 3.

Assessment of association between maternal periodontitis and pre-term low birth weight (PTLBW) infants

Eleven studies[18,20-22,24,26-31] containing data on 2762 participants, of which cases (pregnant women with periodontitis) were (n=1228) and controls (pregnant women without periodontitis) were (n=1534) for the assessment of association between maternal periodontitis with pre-term low birth weight (PTLBW) infants.

As shown in Figure 3 the Odds ratio (OR) is 0.89 (0.46 – 1.72) and the pooled estimates favours cases. This signifies that cases have 0.89 times higher odds of being associated with PTLBW infants as compared to controls and no statistically significant (p=0.73) difference.

On applying random effect model the I^2 statistic showed 93%, the heterogeneity for Tau^2 was 1.03, x^2 being p<0.00001 and the overall effect for Z value being 0.35 (P=0.73).

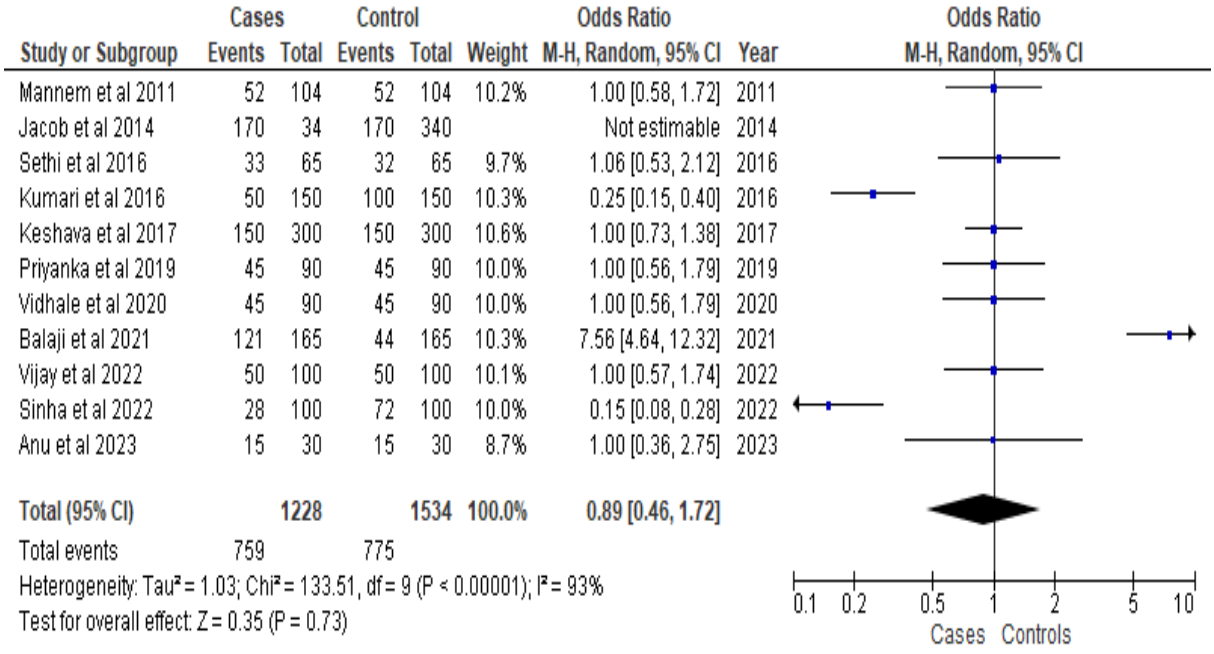

Figure 3: Showing association between maternal periodontitis and pre-term low birth weight (PTLBW) infants

Publication bias

As seen in Figure 4, funnel plot didn't exhibit discernible asymmetry which indicates lack of any publishing bias. The funnel plot displays a symmetrical distribution and a lack of systematic heterogeneity of individual studies when compared with standard error, demonstrating that the meta-analysis was not biased by publication.

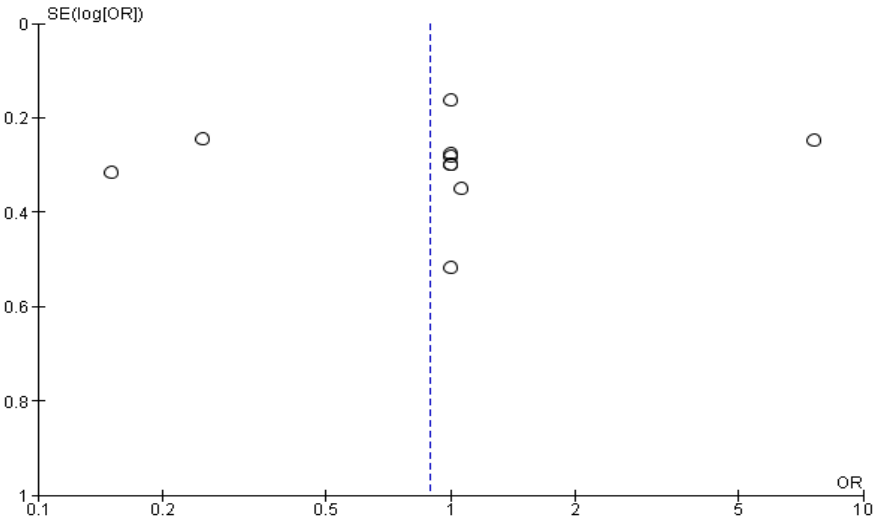

Figure 4: Showing Begg's Funnel plot demonstrating an absence of publication bias

DISCUSSION

This systematic review and meta-analysis was conducted with an aim to provide a comprehensive, qualitative and quantitative analysis of association between maternal periodontitis and PTLBW in Indian scenario. PTLBW is regarded as a frequent obstetric risk factor that contributes to neonatal death and morbidity. Infants with low birth weight are more susceptible to both acute and recurring illnesses. Both periodontitis and PTLBW are multifactorial in nature. Large number of historical, microbiological, experimental and epidemiological evidences have been reported in the last few decades stating, periodontitis as a significant risk for PTLBW globally.[21]

In this study, fourteen case control studies in Indian Population [18-31] which satisfied eligibility criteria were included for systematic review (qualitative analysis) and it was revealed that there is a strong and positive association between maternal periodontitis and PTLBW. However, there is no previous systematic review and meta-analysis in Indian population for the assessment of association between maternal periodontitis and PTLBW. Systematic review by Edwar et al [34] showed a positive association between preterm low birth and maternal periodontitis in Columbian population similar to that of our study, they also summarized the importance of health & education sector's implementation of programs for reducing the incidence of PTLBW. Systematic review and meta-analysis conducted by De Silva[4] in Latin American population showed that maternal age is a major factor in PTLBW which can influence the pregnancy. A systematic review by S. Corbella[9] concluded that there is link between periodontitis and adverse pregnancy outcomes in Italy which is in correlation with our results. Eleven case control studies were then included for meta-analysis (quantitative analysis) and it showed that cases had 0.89 times higher odds (Odds ratio) of being associated with PTLBW infants as compared to controls while all the assessed periodontal parameters were significantly better in controls as compared to cases ($p<0.05$). The results of our study were in accordance with Teshome et al 2016[33] conducted in Ethiopia which summarized that there is an impact of periodontal disease on preterm low birth weight where 12 studies were included in review and summary measures like (OR) and risk ratio (RR) ranging from 2.09 - 4.19 were selected and

evaluated which is similar to conclusion of our study stating that periodontal disease can be potential health risk for PTLBW infants. According to systematic review and meta-analysis conducted in Italy by S. Corbella[9] that estimated an Odd's ratio of 3.0 for PTLBW suggestive of a link between periodontal diseases and adverse pregnancy outcomes.

With the increasing literature & awareness on association of periodontal disease and PTLBW, community health care centers must provide dental camps for prevention against periodontitis or early detection of disease. Organization of health promotion programs through dental campus and educating people on oral hygiene measures and maintenance.

Promotion of oral health is possible by-

a) Promoting health education and maternal and child health centres for pregnant women including dental care.

b) Professional education and awareness by professionals on oral hygiene maintenance.

c) Organizing treatment camps and providing required treatment including complete scaling and root planing for prevention of Periodontal disease.

d) Conducting camps for educating pregnant women about the health problems that can occur leading to PTLBW infants.

However, the role of Periodontitis causing PTLBW is still not clear but the association shows some biologically feasible records. 8Preterm deliveries and periodontal disease are both linked to certain traits.[27] The adherence to the PRISMA guidelines, the thorough unrestricted literature search, utilization of reliable methodology with regards to this qualitative and quantitative synthesis of the data, the quality assessment of evidence with the Cochrane risk of bias tool for randomized controlled trial strengthens this systematic review.[27] All of these studies' quality assessments indicated low to moderate bias risk, but good overall quality, indicating an absence of both possible and inevitable sources of bias with little variation. A systematic review is said to be a transparent and a reproducible method for identifying, selecting and critically evaluating the published literature to answer a well-defined research question. A systematic review is usually combined with a meta-analysis, which provides statistical analysis which combines numerical data. opt out of such studies. The best kind of evidences are regarded to be systematic reviews and meta-analysis. The caliber of the research included, however, is correlated with the strength of evidence used in systematic reviews and meta-analysis.

CONCLUSION

Results indicate that periodontitis in patients during the time of pregnancy is regarded as an important risk factor for PTLBW. Maternal periodontitis is considered to be in association with PTLBW deliveries. For women who posses higher risk of delivering PTLBW infants should be encouraged for early screening & therapy for periodontal disease, before and after conceiving, which can prove to be advantageous. Maintaining proper dental hygiene is important for preventing periodontitis-related negative consequences during pregnancy on the fetus. Therefore, pre-conception treatment should include a routine periodontal examination and appropriate dental hygiene practices should be followed both before and throughout pregnancy.

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