BMJ Open

Dental caries and preterm birth: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018556
Article Type:	Research
Date Submitted by the Author:	07-Jul-2017
Complete List of Authors:	Wagle, Madhu; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine D'Antonio, Francesco; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine Reierth, Eirik; University of Tromso, Science and Health Library Basnet, Purusotam; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine Trovik, Tordis; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Community Medicine Orsini, Giovanna; Universita Politecnica delle Marche, Department of Clinical Sciences and Stomatology Manzoli, Lamberto; University of Ferrara, Department of Medical Sciences Acharya, G; Karolinska Institutet, Center for Fetal Medicine; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Dental caries, pregnancy, pregnant woman, risk, preterm birth, EPIDEMIOLOGY, PUBLIC HEALTH

Tittle page

Dental caries and preterm birth:

A systematic review and meta-analysis

Madhu Wagle[1,*], Francesco D'Antonio[1,2], Eirik Reierth[3], Purusotam Basnet[1,2], Tordis A Trovik[4], Giovanna Orsini[5], Lamberto Manzoli[6], Ganesh Acharya[1,7,8]

[1]Women's Health and Perinatology Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT - The Arctic University of Norway, Tromsø, Norway.

[2]Department of Obstetrics and Gynaecology, University Hospital of Northern Norway, Tromsø, Norway.

[3]Science and Health Library, University Library, UiT The Arctic University of Norway, Tromsø, Norway.

[4]Department of Community Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway.

[5]Department of Clinical Sciences and Stomatology, Polytechnic University of Marche, Ancona, Italy.

[6]Department of Medical Sciences, University of Ferrara, Italy.

[7]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden.

[8]Center for Fetal Medicine, Karolinska University Hospital, Stockholm Sweden.

***Corresponding author** – Madhu Wagle

Women's Health and Perinatology Research Group, Department of Clinical Medicine,

Faculty of Health Sciences,

UiT The Arctic University of Norway,

N – 9037, Tromsø, Norway.

E-mail- madhu.wagle@uit.no

Word Count: Abstract- 186 words, Texts- 2203 words ,

Tables- 3

Figures- 3

Supplementary files- 2

ABSTRACT

Objectives: The primary objective of this systematic review was to explore the association between dental caries and preterm (PTB). The secondary objective was ascertaining the difference between women with dental caries who experienced PTB compared to those who did not with regards to decayed, missing, and filled teeth (DMFT) and decayed, missing, and filled surfaces (DMFS) indices.

Methods: Medline, Embase, Cinahl and Cochrane databases were searched up to March 2017. We included observational cohort and case-control studies. Random-effect meta-analyses were used to compute the summary odds ratio of PTB among women with caries versus women without caries, and the mean difference in either DMFT or DMFS indices between women experiencing PTB compared to those without PTB.

Results: Nine observational studies (4826 pregnancies) were included. Women affected by dental caries during pregnancy did not show a significantly higher risk of PTB (RR: 1.16, 95%CI: 0.90; 1.49, p= 0.25). Also, the women with PTB did not show significantly higher DMFT or DMFS indices (summary mean differences: 1.56, p= 0.10; and -0.15, p= 0.9, respectively).

Conclusion: Dental caries does not appear to be a substantial risk factor for PTB.

PROSPERO Registration number: CRD42017062573

Strengths and limitations of this study

- Strength of the study is its robust methodology. We tried to cover all available studies, access data quality and synthesize suitable data.
- Small number of cases in some of the included studies, their design, different follow-up periods and dissimilarity of the population studies are the limitations.
- Similarly, the lack of description or classification of dental caries stage is another limitation due to which the stratification of analysis according to the disease severity could not be performed.

Keywords: Dental caries, pregnancy, pregnant woman, risk, preterm birth.

INTRODUCTION

Preterm birth (PTB) is the major cause of perinatal mortality and morbidity in the developed countries, with an estimated incidence of 5-13%[1-4]. Although advances in neonatal care have led to a reduction in the neonatal mortality rate, these infants remain at risk of developing a wide array of short and long-term complications such as respiratory, gastrointestinal and neurodevelopmental disabilities[4].

Several risk factors have been associated with PTB; among these, intrauterine infection has emerged as one of the most important factors. Despite this, PTB cannot be considered a unique disease but rather a syndrome characterized by multiple etiology and in which different factors may play a peculiar role[5].

Periodontal disease have been shown to carry an increased risk for PTB; the rationale for this assumption is based upon the fact that periodontitis may lead to maternal and fetal inflammation, thus triggering the common pathway of preterm parturition syndrome including increased uterine contractility, cervical ripening and decidua/membrane activation[6-11]. Although dental caries, defined as a localized destruction of the tooth and its structure by the acidic by-product produced by the bacteria during the dietary carbohydrate fermentation[12], is one of the major oral health problems in developed countries, the effect of dental caries on pregnancy outcome have not been consistently explored. Pregnant women are more susceptible to dental caries and gingivitis compared to their non-pregnant counterparts[13]. Several studies reported that dental caries causing bacteria may have some influence on the pregnancy outcome as PTB and/or low birth weight, while in contrary, the other showed no association between these two factors[14,15].

The primary aim of this systematic review was to explore the association between dental caries and PTB; the secondary aim was to ascertain the differences in dental caries characteristics between women who deliver preterm compared to those who do not deliver preterm.

METHODOLOGY

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[16, 17].

We developed a search strategy, and a systematic literature search was performed in the following databases: Ovid MEDLINE(R) (In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R), Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R), Embase Classic+ (Ovid), The Web of Science® (Thomson Reuters) and The Cochrane Library (Wiley) and CINAHL Plus (EBSCOhost).

The full search was performed in November 2015 and repeated in December 2016. Supplementary material 1 shows the complete search string as it was performed in Medline. The controlled vocabulary of Medical Subject Headings (MeSH) from Medline, and the Emtree thesaurus from Embase, including sub-headings, were used when applicable. In addition, the search fields; title, abstract and key words, were searched when applicable. In The Web of Science, the search fields, title and topic were used. All references were exported to EndnoteTM (x7.4 – Thompson Reuters), where duplicates were removed. There were no restrictions regarding languages or publication year for the searches.

Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed[18].

The study was registered with the PROSPERO database (Registration number: CRD42017062573).

Study selection, data collection and data items

The primary outcome was the occurrence of PTB, defined as birth <37 weeks of gestation. We aimed to stratify the analysis according the type of PTB (spontaneous vs iatrogenic) and according to gestational age at birth (moderate to late preterm (<34 weeks), very preterm (<32 weeks) and extremely preterm <28 weeks)[19].

The secondary outcome was to ascertain the difference between women with dental caries who experienced PTB compared to those who did not experience PTB in either decayed, missing, and filled teeth (DMFT) or decayed, missing, and filled surfaces (DMFS) indices[20].

DMFT and DMFS indices are numerical expression of the caries prevalence of an individual or groups and is widely used in epidemiological surveys of oral health. DMFT/DMFS is calculated by adding up permanent teeth that are caries affected wherein D is for decay, M is missing due to caries and F is filled teeth (T) or surfaces (S). If one tooth has filling as well as caries lesion, then it is counted as D for DMFT index whereas filling+caries surface is counted as D but if there is F on one and D in other surface, then they are counted differently for DMFS index. The anterior teeth up to canine have 4 and pre-molars and molars teeth have 5 surfaces, respectively in DMFS index. D+M+F = caries prevalence of an individual [maximum of 28 for DMFT and 128 for DMFS, if 28 permanent teeth are included (excluding 4 wisdom molar teeth)][20, 21].

Studies were assessed according to the following criteria: population, outcome, gestational age at birth and clinical characteristics of the caries during pregnancy.

Two authors (MW, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed among the reviewers and consensus reached. Any dispute was resolved by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS)[22]; according to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered

item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability[22].

Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases were also excluded to avoid publication bias.

Statistical analysis

A first random-effect meta-analysis of binary outcomes was used to compute the summary odds ratio (and relative 95% confidence interval - CI) of preterm birth (PTB) among women with caries versus women without caries (controls).

Other two meta-analyses evaluated continuous outcomes: decayed, missing and filled teeth (DMFT), and decayed, missing and filled surfaces (DMFS). As the included studies did not differ in their outcome definitions, we used a random-effect approach to compute the mean difference in either DMFT or DMFS between PTB and non-PTB. In one study by Martinez-Martinez, the standard deviations were not available, and we thus conservatively used the largest values recorded in the other included studies.

For all meta-analyses, the heterogeneity across studies was quantified using I^2 statistic, and all computations were made using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

General characteristics

A total of 1786 articles were identified, 20 were assessed with respect to their eligibility for inclusion (Supplementary Material 2) and 9 studies were included in the systematic review (Table 1, Figure 1). These 9 studies included 4826 pregnancies.

Results of quality assessment of the included studies using NOS for cohort studies are presented in Table 2. Most of the included studies showed an overall good rate about the selection and comparability of the study groups, and for the ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size with even smaller number of events (PTB) and different gestational ages at assessment.

Synthesis of the results

Five studies explored the risk of PTB in women who compared to those who did not have caries during pregnancy and reported that women affected by caries in pregnancy did not have an increased risk of delivering <37 weeks of gestation (RR: 1.16, 95% CI 0.90; 1.49, p= 0.25; I^2: 34%). (Figure 2).

There was no difference in either DMFT (1.56, 95% CI -0.28; 3.41, p= 0.10) and DMFS (-0.15 (-3.40; 3.09, p= 0.9) (Table 3) (Figure 3).

Due to very small number of included cases and lack of information from the original study, it was not possible to perform any sub-analysis according to different gestational age at birth and type of PTB (spontaneous vs iatrogenic).

DISCUSSIONS

Summary of evidence

The findings from this systematic review showed that pregnant women with dental caries are not at increased risk for PTB. Furthermore, there was no difference in the mean DMFT and DMFS indices between women with dental caries who experienced PTB compared to those who did not.

Strength and limitations

The strength of this meta-analysis is its robust methodology. We tried to cover all available studies, access the quality of the data and synthesize all suitable data.

The small number of cases in some of the included studies, their retrospective non-randomized design, different periods of follow-up, dissimilarity of the populations studies (due to various inclusion criteria) and lack of standardized criteria for the antenatal management of pregnancies with dental caries represent the major limitations of this systematic review. The lack of description or classification of caries stage in the studies included is other limitation of our review and it was not possible to stratify the analysis according to the severity of the disease. Assessment of the potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the small number of individual studies, which strongly limits the reliability of formal tests.

Implication for clinical practice

The consequences of overall oral health including the oral health in pregnant women is of a great concern[23]. Dental caries and periodontal disease are the most common oral diseases worldwide. The higher prevalence of gingival alterations during pregnancy, especially bleeding during brushing, is a problem that is commonly encountered by pregnant women. Properly maintained oral hygiene care is known to have an impact on the oral health of pregnant women[24, 25] and availability of free dental care also appears to influence this[26]. Whereas in contrast, if proper oral hygiene is not maintained during pregnancy, the chances to develop oral health problems as enamel erosions, dental caries[27] and gingivitis increases.

There are no reports indicating that the incidence of dental caries increases during pregnancy, but it has been suggested that the chances of getting dental caries increases because of the change in

diet, frequent snacking due to food craving and poor oral health[28]. Furthermore, the prevalence of dental caries seemed to be higher in older pregnant women[29]. Despite the high caries prevalence in most developed countries, very few studies have explored the potential association between oral health and adverse pregnancy outcome.

Identification of women at higher risk of PTB is fundamental to prevent the likelihood of delivering preterm. Several risk factors as been associated with PTB, such as prior history of PTB, cervical disease and infection. Despite this, finding an association between a given risk factor and the occurrence of PTB is challenging.

Dental caries is a frequently encountered oral health problem in pregnancy as pregnant women are more susceptible to caries compared to non-pregnant women[13]. Being caused by an infectious process, caries can theoretically lead to inflammation and thus increase the risk of PTB[12]. Despite this, we could not find any significant association between dental caries and PTB; furthermore, we did not find any significant difference in the severity of caries assessed by DMFT and DMFS indices between women who experienced PTB compared to those who did not.

The lack of association between dental caries and PTB is difficult to explain. The initiation and progression of the caries lesion is very slow and the destruction caused by caries in initial stage can be reversible[12]. In addition to this, pregnancy itself does not cause dental caries but it may exacerbate the existing condition. Dental caries is symptomless until there is severe and irreversible destruction of teeth[30]. It might be possible that bacterial spreading during caries formation and the subsequent production of pro-inflammatory mediators induced by oral pathogens may not be of the magnitude to cause production of pro-inflammatory mediators enough to initiate PTB.

Even though we found no significant relationship between the dental caries and PTB, the risk of transmitting the oral cariogenic flora from the mother to her infant and predisposing the infant to dental caries in the future should not be neglected[31-34]. Therefore, large prospective studies aiming at ascertaining the association between dental caries and spontaneous PTB, according to the gestational age at occurrence, severity of the disease and presence of other co-morbidities are needed in order to elucidate the role, if any, of dental caries in increasing the risk of PTB.

REFERNCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
2. Slattery MM, Morrison JJ. Preterm delivery. Lancet. 2002;360(9344):1489–97.
3. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med. 1985;312(2):82–90.
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-9.
5. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG. 2006;113(Suppl 3):S17-42.
6. Jeffcoat MK, Geurs NC, Reddy MS, Goldenberg RL, Hauth JC. Current evidence regarding periodontal disease as a risk factor in preterm birth. Ann Periodontol. 2001;6:183–88.
7. Offenbacher S. Maternal periodontal infections, prematurity, and growth restriction. Clin Obstet Gynecol. 2004;47:808–21.
8. Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol. 2006;107(1):29–36.
9. Jarjoura K, Devine PC, Perez-Delboy A, Herrera-Abreu M, D'Alton M, Papapanou PN. Markers of periodontal infection and preterm birth. Am J Obstet Gynecol. 2005;192:513–19.
10. Goepfert AR, Jeffcoat MK, Andrews WW, Faye-Petersen O, Cliver SP, Goldenberg RL, et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol. 2004;104(4):777–83.
11. Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG. 2006;113:135–43.
12. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007;369(9555):51-9.
13. Martinez-Beneyto Y, Vera-Delgado MV, Perez, L, Maurandi A. Self-reported oral health and hygiene habits, dental decay, and periodontal condition among pregnant European women. Inl J Gynecol Obstet. 2011;114(1):18-22.
14. Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ. Salivary Actinimyces naeslundii genospecies 2 and Lactobacillus casei level predicts pregnancy outcome. J Periodontol. 2005;76(2):171-77.
15. Durand R, Gunselman EL, Hodges JS, DiAngelis AS, Michalowicz BS. A pilot study of the association of cariogenic bacteria and preterm birth. Oral Dis. 2009;15(6):400-06.
16. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton) 2010;15(6):617–24.
17. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK). 2009.
18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015

statement. Syst Rev 2015;4:1. Available at http://www.prisma-statement.org/ [accessed 20 April 2017].
19. World Health Organization. Preterm birth. 2017 [online] Available at http://www.who.int/mediacentre/factsheets/fs363/en/ [Accessed 3 May 2017].
20. World Health Organization. Oral health surveys: basic methods. 4th ed. 1997 Geneva.
21. Malmo University. Caries prevalence and Calculation. 2010 [online] Available at https://www.mah.se/CAPP/Methods-and-Indices/for-Caries-prevalence/ [Accessed 11 April 2017]
22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. [Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 3 May 2017]
23. Achtari MD, Georgakopoulou EA, Afentoulide N. Dental care throughout pregnancy: what a dentists must know. Oral Health Dent Manag. 2012;11(4):169-76.
24. Huebner CE, Milgrom P, Conrad, D. et al. Providing dental care to pregnant patients: a survey of Oregon general dentists. J Am Dent Assoc. 2009;140(2):211-22.
25. Boggess KA, Urlaub DM, Massey KE, Moos MK, Matheson MB, Lorenz C. Oral hygiene practice and dental service utilization among pregnant women. J Am Dent Assoc. 2010;141(5): 553-61.
26. Hulla E, Turok Y, Nauta M, Yoong W. Self-reported oral hygiene habits, dental attendance and attitudes to dentistry during pregnancy in a sample of immigrant women in North London. Arch Gynecol Obstet. 2008;277(5):405-09.
27. Merglova V, Hecova H, Stehlikova J, Chaloupka P (2012) Oral health status of women with high-risk pregnancies. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2012; 156(4):337-41.
28. Gajendra S, Kumar JV. Oral health and pregnancy: a review. N Y State Dent J. 2004;70(1): 40-4.
29. Shamsi M, Hidarnia A, Niknami S, Khorsandi M. The status of dental caries and some acting factors in a sample of Iranian women with pregnancy. World J Med Sci. 2013;9(4):190-97. ISSN 1817-3055. DOI: 10.5829/idosi.wjms.2013.9.4.76161
30. Kloetzel MK, Huebner CE, Milgrom P. Referrals for dental care during pregnancy. J Midwifery Womens Health. 2011;56(2):110-17.
31. Zanata RL, Navarro MF, Pereira JC, Franco EB, Lauris JR, Barbosa SH. Effect of caries preventive measures directed to expectant mothers on caries experience in their children. Braz Dent J. 2003;14(2):75-81.
32. Goldie MP. Oral health care for pregnant and postpartum women. Int J Dent Hyg. 2003;1(3):174-6.
33. Boggess KA, Edelstein BL. Oral health in women during preconception and pregnancy: implications for birth outcomes and infant oral health. Matern Child Health J. 2006;10 (5 Suppl):S169-74.
34. Boggess KA, Society for Maternal-Fetal Medicine Publications Committee. Maternal oral health in pregnancy. Obstet Gynecol. 2008;111(4):976-86.

TABLES

Table 1. General characteristics of the included studies.

Author	Year	Country	Period analyzed (y)	Study design	Gestational age at dental examination	Number of subject (n)	Definition of PTB
Martinez-Martinez	2016	Mexico	2013-2014	Retrospective	From the first trimester of pregnancy until 8 weeks postpartum	70	<37 weeks
Durand	2015	France	2005-2006	Prospective	Within 8 weeks after delivery	107	<37 weeks
Harjunmaa	2015	Malawi	2011-2013	Prospective	Within 6 weeks after delivery	1024	<37 weeks
Acharya	2013	India	2009	Retrospective	Within 1 day after delivery	316	<37 weeks
Vergnes	2011	France	2003-2006	Retrospective	Within 2–4 days post-partum	2201	<37 weeks
Ryalat	2011	Jordan	2009	Prospective	Within 1 week post-partum	200	<37 weeks
Heimonen	2008	Finland	2002-2004	Retrospective	Within 2 days post-partum	328	<37 weeks
Mumghamba	2007	Tanzania	NS	Retrospective	Within 40 days from delivery	373	<37 weeks
Meurman	2006	Finland	1998-2000	Retrospective	From the first trimester of pregnancy	207	<37 weeks

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Martinez-Martinez	2016	★★	★	★
Durand	2016	★★★	★★	★★
Harjunmaa	2015	★★	★	★
Acharya	2015	★★	★	★★
Vergnes	2015	★★★	★★	★
Ryalat	2015	★★★	★	★★
Heimonen	2014	★★	★	★
Mumghamba	2010	★★	★	★
Meurman	2009	★★	★	★

Table 3. Selected outcomes evaluating the association between caries and preterm birth.

Outcomes	**N. studies (n/N)**	**Odds Ratio (95% CI)**	**p**	**I^2, %**
Preterm birth (PTB), women with caries versus controls	5 (1472/4246)	1.16 (0.90; 1.49)	0.25	35
	N. studies (n/N)	**Mean difference (95% CI)**	**p**	**I^2, %**
DMFT (PTB versus Non-PTB)	5 (2963)	1.56 (-0.28; 3.41)	0.10	92
DMFS (PTB versus Non-PTB)	3 (2594)	-0.15 (-3.40; 3.09)	0.9	89

CI: Confidence interval. n: number of events. N: total number of participants. DMFT: Decayed, missed, and filled teeth. DMFS: Decayed, missed, and filled surface.

FIGURES

Figure 1. Systematic review flowchart

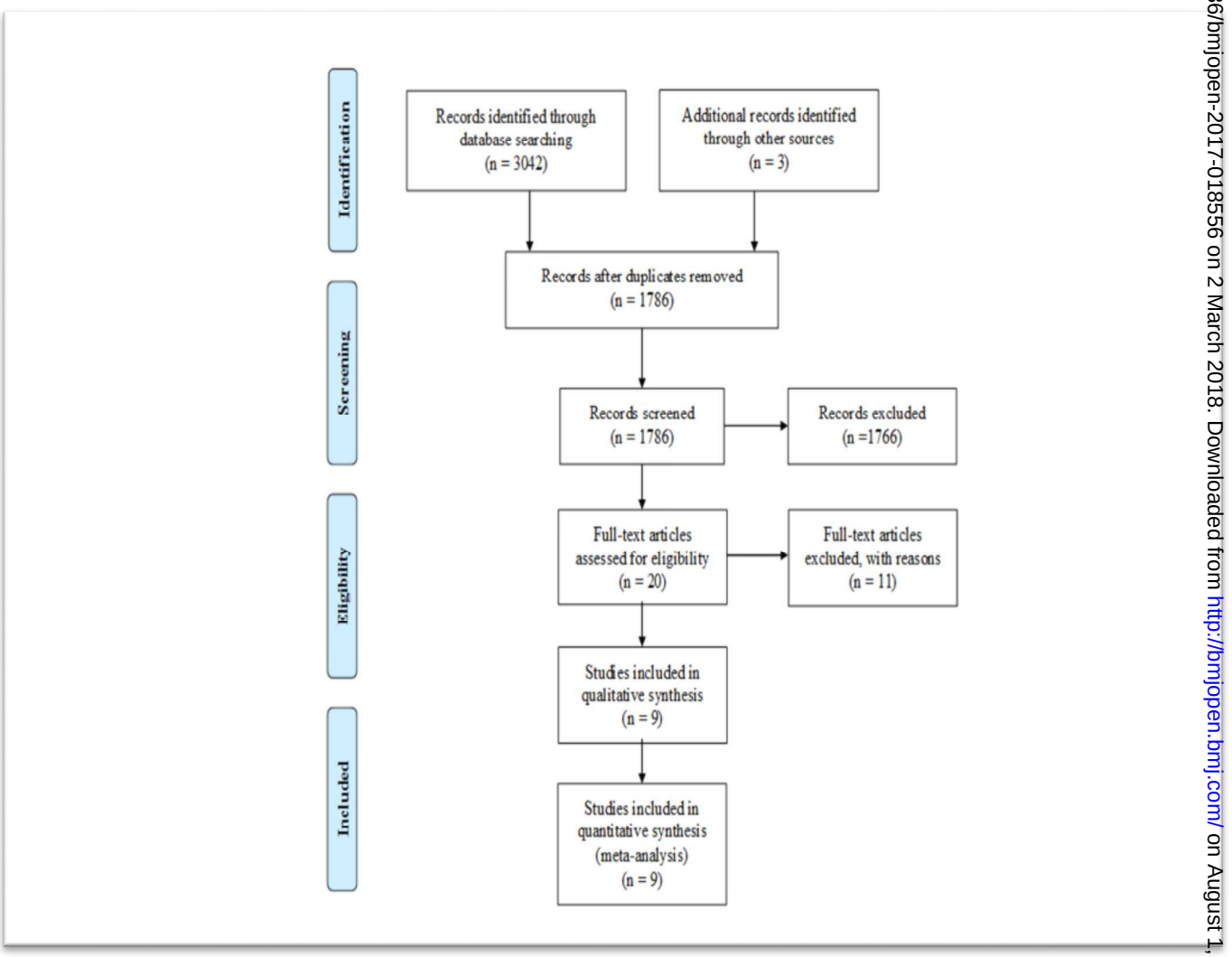


Figure 2. Pooled odd ratio (OR) for the risk of preterm birth (PTB) in women compared with those without caries.

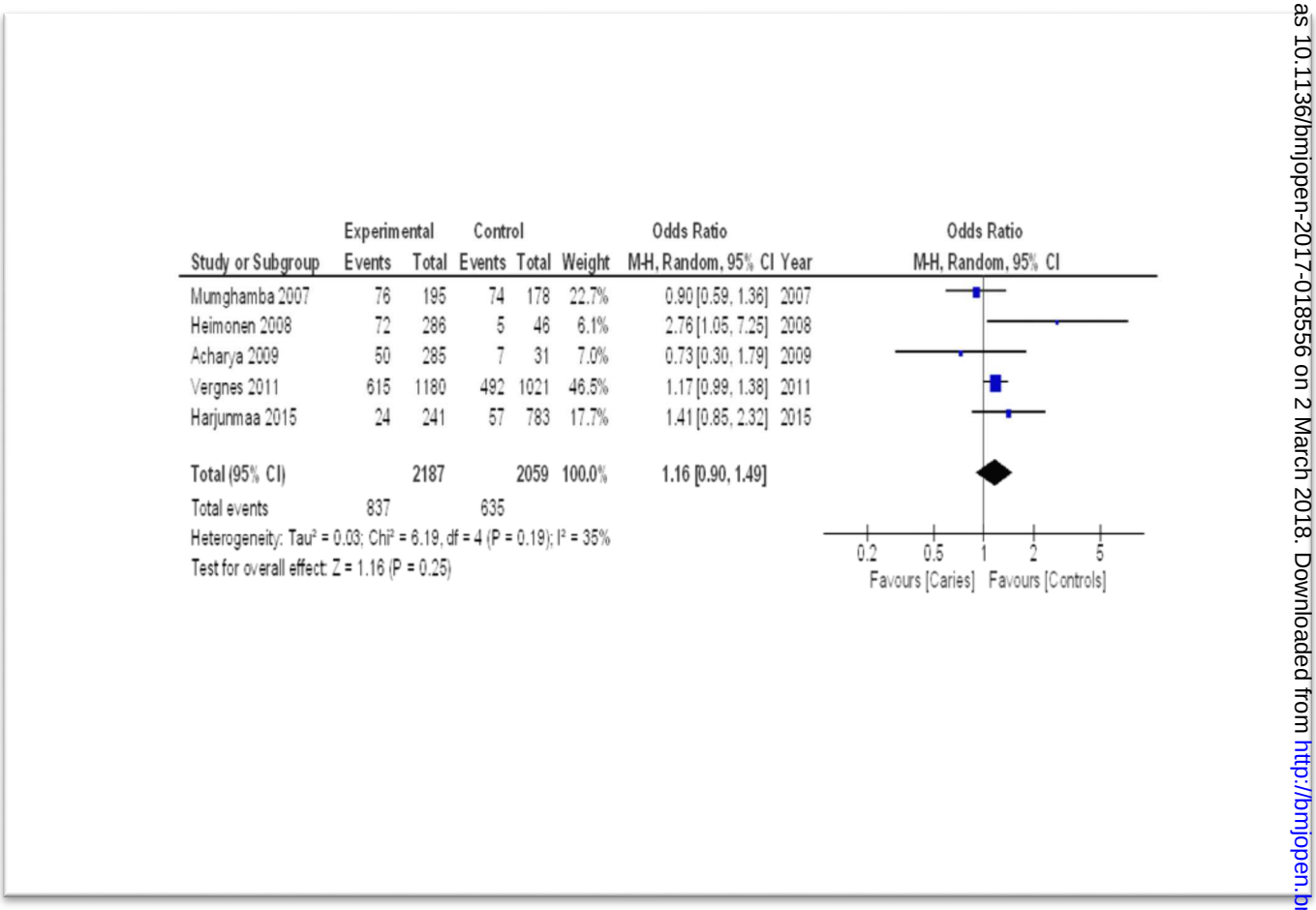
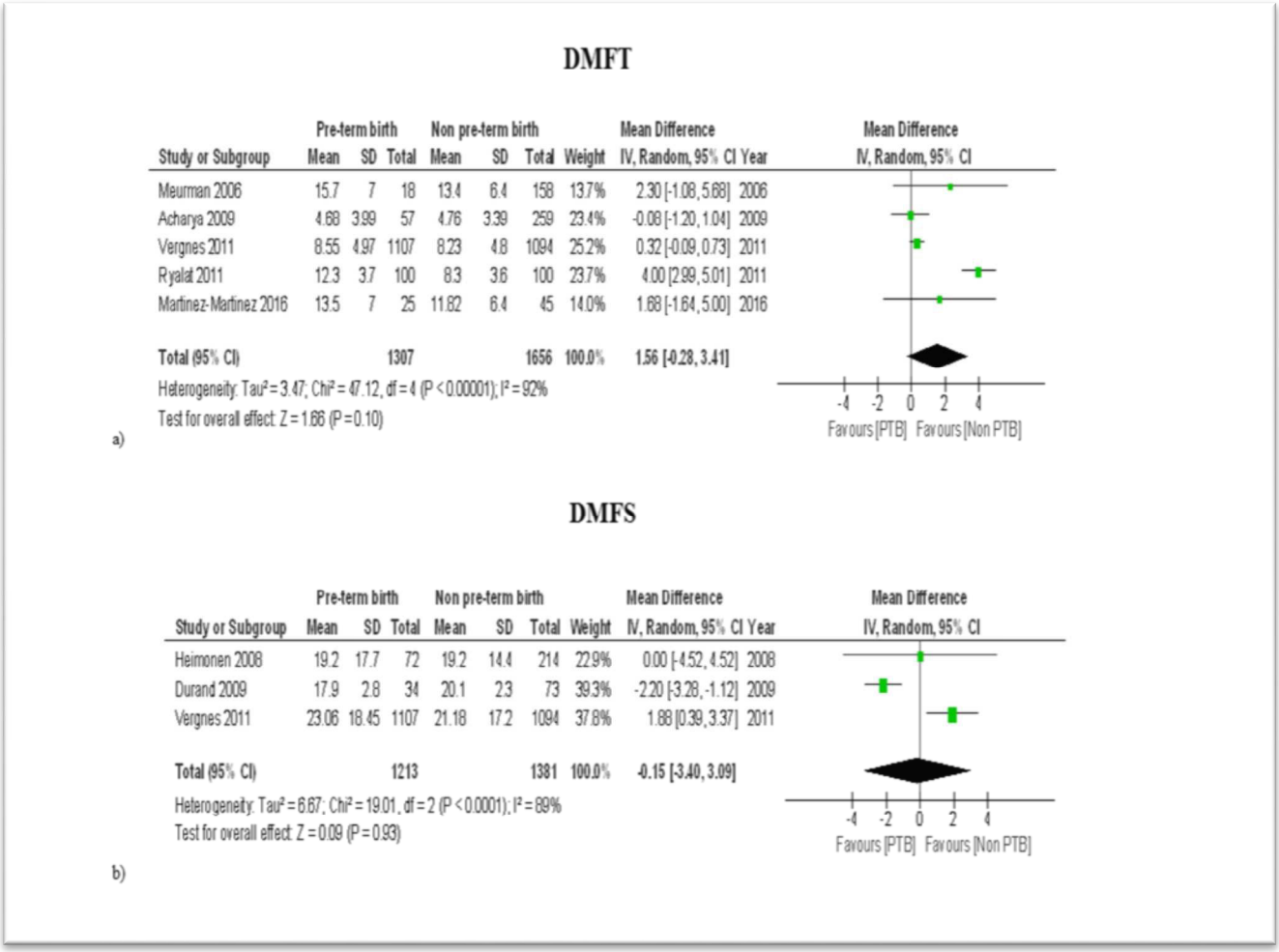


Figure 3. Mean differences in DMFT and DMFS indices in women with caries compared to those who did not experience PTB.



FUNDING

No funding was received for the conduction of this review.

The publication charges for this article have been funded by a grant from the publication fund of UiT The Arctic University of Norway.

CONTRIBUTORS

Study concept, design and methodology - MW, GA, FD'A, ER

Data Collection and entry - ER

Abstracts and articles review - MW, FD'A

Analysis and interpretation of data - F'DA, MW, GO, LM

Supervision - FD'A, GA, PB, TAT

Writing, review, critique, comments and revision of manuscript- MW, FD'A, ER, TAT, PB, GO, LM, GA

ACKNOWLEDGEMENT

We would sincerely like to thank Prof. S Acharya, Prof. S Abati, Prof. I Cetin, Prof. GG Campus, Prof. A Villa, Prof. R Martinez, Prof. S Ryalat, Prof. JH Meurman, Prof. Y Khader, Prof. A Heimonen, Prof. U Harjunmaa, Prof. R Durand, Prof. N Buduneli and Prof. AP Dasanayake for their co-operation and contribution by providing additional data and necessary information for this systemic review.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data is available.

ABBREVIATION

DMFS – Decayed, Missing, Filled Surface

DMFT- Decayed, Missing, Filled Teeth

NOS - Newcastle-Ottawa Scale

PTB – Preterm Birth

Supplementary material 1

Supplementary Table 2. Excluded studies and reason for the exclusion.

Author	Year	Title	Reason for the exclusion
Saraiva	2007	Are intrauterine growth restriction and preterm birth associated with dental caries?	No data on caries in pregnancy
Shulman	2005	Is There an Association between Low Birth Weight and Caries in the Primary Dentition?	No data on caries in pregnancy
Saraiva	2009	Intrauterine Growth Restriction and Preterm Birth Were not Associated with Primary Teeth Caries	No data on caries in pregnancy
Sayyed	2014	The relationship between term pre-eclampsia and the risk of early childhood caries	No data on caries in pregnancy
Merglova	2012	Oral health status of women with high-risk pregnancies	No data on the outcomes explored in this systematic review
Dasanayake	2005	Salivary Actinomyces naeslundii Genospecies 2 and Lactobacillus casei Levels Predict Pregnancy Outcomes	No data on the outcomes explored in this systematic review
Khader	2007	Risk Indicators of Pre-Eclampsia in North Jordan: Is Dental Caries Involved?	No data on caries and PTB
Bosniak	2006	Pre-term delivery and periodontal disease: a case–control study from Croatia	No data on the outcomes explored in this systematic review
Budeli	2005	Periodontal infections and pre-term low birth weight: a case-control study	The number of decayed teeth were provided as a continuous variable; thus it was not possible to extrapolate any data regarding the occurrence of PTB in women with compared to those without caries. Furthermore, no information on the DFMT score was provided by the authors.
Durand	2009	A pilot study of the association between cariogenic oral bacteria and preterm birth	It was not possible to extrapolate data regarding the occurrence of PTB in pregnancies with compared to those without caries; furthermore, it was not possible to extract any information regarding the mean DMFT values in women who compared to those who did not deliver preterm
Abati	2012	Lack of association between maternal periodontal status and adverse pregnancy outcomes: a multicentric epidemiologic study	It was not possible to extrapolate data regarding the occurrence of PTB in pregnancies with compared to those without caries; furthermore, it was not possible to extract any information regarding the mean DMFT values in women who compared to

			those who did

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Dental caries and preterm birth: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018556.R1
Article Type:	Research
Date Submitted by the Author:	24-Nov-2017
Complete List of Authors:	Wagle, Madhu; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine D'Antonio, Francesco; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine Reierth, Eirik; University of Tromso, Science and Health Library Basnet, Purusotam; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine Trovik, Tordis; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Community Medicine Orsini, Giovanna; Universita Politecnica delle Marche, Department of Clinical Sciences and Stomatology Manzoli, Lamberto; University of Ferrara, Department of Medical Sciences Acharya, G; Karolinska Institutet, Center for Fetal Medicine; Universitetet i Tromso Helsevitenskapelige fakultet Helsefak, Department of Clinical Medicine
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Dental caries, pregnancy, pregnant woman, risk, preterm birth, EPIDEMIOLOGY, PUBLIC HEALTH

Tittle page

Dental caries and preterm birth:

A systematic review and meta-analysis

Madhu Wagle[1,*], Francesco D'Antonio[1,2], Eirik Reierth[3], Purusotam Basnet[1,2], Tordis A Trovik[4], Giovanna Orsini[5], Lamberto Manzoli[6], Ganesh Acharya[1,7,8]

[1]Women's Health and Perinatology Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT - The Arctic University of Norway, Tromsø, Norway.

[2]Department of Obstetrics and Gynaecology, University Hospital of Northern Norway, Tromsø, Norway.

[3]Science and Health Library, University Library, UiT The Arctic University of Norway, Tromsø, Norway.

[4]Department of Community Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway.

[5]Department of Clinical Sciences and Stomatology, Polytechnic University of Marche, Ancona, Italy.

[6]Department of Medical Sciences, University of Ferrara, Italy.

[7]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden.

[8]Center for Fetal Medicine, Karolinska University Hospital, Stockholm Sweden.

***Corresponding author** – Madhu Wagle

Women's Health and Perinatology Research Group, Department of Clinical Medicine,

Faculty of Health Sciences,

UiT The Arctic University of Norway,

N – 9037, Tromsø, Norway.

E-mail- madhu.wagle@uit.no

Word Count: Abstract- 220 words, Texts- 2431 words ,

Tables- 3

Figures- 3

Supplementary files- 3

ABSTRACT

Objectives: The primary objective of this systematic review was to evaluate the association between dental caries and preterm birth (PTB). The secondary objective was ascertaining the difference between women with dental caries who experienced PTB compared to those who did not with regards to decayed, missing, and filled teeth (DMFT) and decayed, missing, and filled surfaces (DMFS) indices.

Methods: Medline, Embase, Cinahl and Cochrane databases were searched initially in November 2015 and repeated in December 2016. We included observational cohort and case-control studies. Only studies reporting the risk of PTB in women affected compared to those not affected by dental caries in pregnancy were included. Random-effect meta-analyses were used to compute the summary odds ratio of PTB among women with caries versus women without caries, and the mean difference in either DMFT or DMFS indices between women experiencing PTB compared to those without PTB.

Results: Nine observational studies (4826 pregnancies) were included. Women affected by dental caries during pregnancy did not show a significantly higher risk of PTB [OR: 1.16, 95%CI (0.90, 1.49), p= 0.25, I^2 =35%]. Also, the women with PTB did not show significantly higher DMFT or DMFS indices (summary mean differences: 1.56, p= 0.10; I^2 =92% and -0.15, p= 0.9, I^2 =89%, respectively).

Conclusion: Dental caries does not appear to be a substantial risk factor for PTB.

PROSPERO Registration number: CRD42017062573

Strengths and limitations of this study

- Strength of the study is its robust methodology. We tried to cover all available studies, access data quality and synthesize suitable data.
- Small number of cases in some of the included studies, their design, different follow-up periods and dissimilarity of the population studies are the limitations.
- Similarly, the lack of description or classification of dental caries stage is another limitation due to which the stratification of analysis according to the disease severity could not be performed.

Keywords: Dental caries, pregnancy, pregnant woman, risk, preterm birth.

INTRODUCTION

Preterm birth (PTB) is the major cause of perinatal mortality and morbidity in the developed countries, with an estimated incidence of 5-13%[1-4]. Although advances in neonatal care have led to a reduction in the neonatal mortality rate, infants born prematurely remain at risk of developing a wide array of short and long-term complications such as respiratory, gastrointestinal and neurodevelopmental disabilities[4].

Several risk factors have been associated with PTB[1,5]; among these, intrauterine infection has emerged as one of the most important factors. Despite this, PTB cannot be considered a unique disease but rather a syndrome characterized by multiple etiology and in which different factors may play a peculiar role[5].

Periodontal disease has been shown to carry an increased risk for PTB; the rationale for this association is based on the suggestion that periodontitis may lead to maternal and fetal inflammation, thus triggering the common pathway of preterm parturition syndrome including increased uterine contractility, cervical ripening and decidua/membrane activation[6-11]. Although dental caries, defined as a localized destruction of the tooth and its structure by the acidic by-product produced by the bacteria during the dietary carbohydrate fermentation[12], is one of the major oral health problems in developed countries, the effect of dental caries on pregnancy outcome have not been consistently explored. Pregnant women are more susceptible to dental caries and gingivitis compared to their non-pregnant counterparts[13] because of the change in their diet, frequent snacking due to food craving and oral health negligance[14]. If left untreated, dental caries may result in further inflammatory complications[15], which could influence pregnancy outcomes. Several studies reported that dental caries causing bacteria may have some influence on the pregnancy outcome as PTB and/or low birth weight, while in contrary, the other showed no association between these two factors [16-27].

The primary aim of this systematic review was to explore the association between dental caries and PTB; the secondary aim was to ascertain the differences in dental caries characteristics between women who deliver preterm compared to those who do not deliver preterm.

METHODOLOGY

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[28,29].

We developed a search strategy, and a systematic literature search was performed in the following databases: Ovid MEDLINE(R) (In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R), Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R), Embase Classic+ (Ovid), The Web of Science® (Thomson Reuters) and The Cochrane Library (Wiley) and CINAHL Plus (EBSCOhost).

The full search was performed in November 2015 and repeated in December 2016. Supplementary material 1 shows the complete search string as it was performed in Medline. The controlled vocabulary of Medical Subject Headings (MeSH) from Medline, and the Emtree thesaurus from Embase, including sub-headings, were used when applicable. In addition, the search fields; title, abstract and key words, were searched when applicable. In The Web of Science, the search fields, title and topic were used. All references were exported to EndnoteTM (x7.4 – Thompson Reuters), where duplicates were removed. There were no restrictions regarding languages or publication year for the searches.

Reference lists of relevant articles and reviews were hand searched for additional reports. MOOSE guidelines were followed[30].

The study was registered with the PROSPERO database (Registration number: CRD42017062573).

Study selection, data collection and data items

We aimed to compare the incidence of preterm birth among the pregnant women population with dental caries to those who do not have dental caries.

The primary outcome was the occurrence of PTB, defined as birth <37 weeks of gestation. We aimed to categorise the analysis according the type of PTB (spontaneous vs iatrogenic vs term) and according to gestational age at birth (moderate to late preterm (32 to <37 weeks), very preterm (28 to <32 weeks) and extremely preterm <28 weeks[31].

The secondary objective was to ascertain the difference between women with dental caries who experienced PTB compared to those who did not experience PTB in either decayed, missing, and filled teeth (DMFT) or decayed, missing, and filled surfaces (DMFS) indices[32].

DMFT and DMFS indices are numerical expression of the caries prevalence of an individual or groups and is widely used in epidemiological surveys of oral health. DMFT/DMFS is calculated by adding up permanent teeth that are caries affected wherein D is for decay, M is missing due to caries and F is filled teeth (T) or surfaces (S). If one tooth has filling as well as caries lesion, then it is counted as D for DMFT index whereas filling+caries surface is counted as D but if there is F on one and D in other surface, then they are counted differently for DMFS index. The anterior teeth up to canine have 4 and pre-molars and molars teeth have 5 surfaces, respectively in DMFS index. D+M+F = caries prevalence of an individual [maximum of 28 for DMFT and 128 for DMFS, if 28 permanent teeth are included (excluding 4 wisdom molar teeth)][32, 33].

Studies were assessed according to the following criteria: population, outcome, gestational age at birth and clinical characteristics of the caries during pregnancy. Observational cohort and case-control studies were included. Similarly, studies reporting the occurrence of PTB in women affected compared to those not affected by dental caries in pregnancies and the full text articles were considered suitable for the inclusion in the present systematic review. Case reports, conference abstracts and case series with fewer than 3 cases were also excluded to avoid publication bias.

Two authors (MW, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed among the reviewers and consensus reached. Any dispute was resolved by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS)[34]; according to NOS, each study is judged on three broad perspectives: the selection of the

study groups; the comparability of the groups; and ascertainment outcome of interest. An assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. The NOS tool for the quality assessment of the studies is provided in supplementary material 2. According to the tool, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability[34].

Statistical analysis

A first random-effect meta-analysis of binary outcomes was used to compute the summary odds ratio (and relative 95% confidence interval - CI) of preterm birth (PTB) among women with caries versus women without caries (controls).

Other two meta-analyses evaluated continuous outcomes: decayed, missing and filled teeth (DMFT), and decayed, missing and filled surfaces (DMFS). As the included studies did not differ in their outcome definitions, we used a random-effect approach to compute the mean difference in either DMFT or DMFS between PTB and non-PTB. In one study by Martinez-Martinez, the standard deviations were not available, and we thus conservatively used the largest values recorded in the other included studies.

For all meta-analyses, the heterogeneity across studies was quantified using I^2 statistic, and all computations were made using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

General characteristics

A total of 1786 articles were identified, 20 were assessed with respect to their eligibility for inclusion (Supplementary Material 3) and 9 studies were included in the systematic review (Table 1, Figure 1). These 9 studies included 4826 pregnancies.

Results of quality assessment of the included studies using NOS for cohort studies are presented in Table 2. Most of the included studies scored at least 1 star in each of the three categories: the selection and comparability of the study groups, and ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size with even smaller number of events (PTB) and different gestational ages at assessment.

Synthesis of the results

Five studies explored the risk of PTB in women who had caries compared to those who did not have caries during pregnancy and reported that women affected by caries in pregnancy did not have an increased risk of delivering <37 weeks of gestation [OR: 1.16, 95% CI (0.90, 1.49), p= 0.25; I^2: 35%). (Figure 2).

Stratification according to DMFT and DMFS indices to evaluate the association between caries and preterm birth was performed only by five and three studies, respectively. There was no difference in either DMFT [1.56, 95% CI (-0.28, 3.41), p= 0.10] and DMFS [-0.15, 95%CI (-3.40, 3.09), p= 0.9] (Table 3) (Figure 3).

Due to very small number of included cases and lack of information from the original study, it was not possible to perform any sub-analysis according to different gestational age at birth and type of PTB (spontaneous vs iatrogenic vs term).

DISCUSSIONS

Summary of evidence

The findings from this systematic review showed that pregnant women with dental caries are not at increased risk for PTB. Furthermore, there was no difference in the mean DMFT and DMFS indices between women with dental caries who experienced PTB compared to those who did not.

Strength and limitations

This is, to our knowledge, the first systematic review exploring the strength of association between dental caries and PTB. The strength of this meta-analysis is its robust methodology. We tried to cover all available studies, access the quality of the data and synthesize all suitable data. The small number of cases in some of the included studies, their retrospective non-randomized design, different periods of follow-up, dissimilarity of the populations studies (due to various inclusion criteria) and lack of standardized criteria for the antenatal management of pregnancies with dental caries represent the major limitations of this systematic review. Lack of data on early PTB, which is typically associated with infection and inflammation, was another major limitation of the present systematic review. Furthermore, we could not stratify the analysis according to maternal characteristics and caries stage at diagnosis in view of the lack of such information in the large majority of included studies. Assessment of the potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the small number of individual studies, which strongly limits the reliability of formal tests. Finally, statistical heterogeneity among the included studies was another major limitation of the present review which may potentially bias the study findings. In view of these limitations, the findings from this systematic review should be interpreted with cautions.

Implication for clinical practice

The consequences of overall oral health including the oral health in pregnant women is of a great concern[35]. Dental caries and periodontal disease are the most common oral diseases worldwide. The higher prevalence of gingival alterations during pregnancy, especially bleeding during brushing, is a problem that is commonly encountered by pregnant women. Properly maintained oral hygiene care is known to have an impact on the oral health of pregnant women[36, 37] and

availability of free dental care also appears to influence this[38]. Whereas in contrast, if proper oral hygiene is not maintained during pregnancy, the chances to develop oral health problems as enamel erosions, dental caries[39] and gingivitis increases.

There are no reports indicating that the incidence of dental caries increases during pregnancy, but the chances of getting dental caries could increase[14] and the prevalence of dental caries seemed to be higher in older pregnant women[40]. Despite the high dental caries prevalence in most developed countries, very few studies have explored the potential association between oral health and adverse pregnancy outcome.

Identification of women at higher risk of PTB is fundamental to prevent the likelihood of delivering preterm. Several risk factors as been associated with PTB, such as prior history of PTB, cervical disease and infection. Despite this, finding an association between a given risk factor and the occurrence of PTB is challenging.

Dental caries is a frequently encountered oral health problem in pregnancy as pregnant women are more susceptible to caries compared to non-pregnant women[13]. Being caused by an infectious process, dental caries can theoretically lead to inflammation and thus increase the risk of PTB[12]. Despite this, we could not find any significant association between dental caries and PTB; furthermore, we did not find any significant difference in the severity of caries assessed by DMFT and DMFS indices between women who experienced PTB compared to those who did not. In addition to this, since most of these studies have evaluated women after delivery, this may also have influenced the results.

The lack of association between dental caries and PTB is difficult to explain. The initiation and progression of the caries lesion is very slow and the destruction caused by caries in initial stage can be reversible[12]. In addition to this, pregnancy itself does not cause dental caries but it may exacerbate the existing condition. Dental caries is symptomless until there is severe and irreversible destruction of teeth[41]. It might be possible that bacterial spreading during caries formation and the subsequent production of pro-inflammatory mediators induced by oral pathogens may not be of the magnitude to cause production of pro-inflammatory mediators enough to initiate PTB.

Even though we found no significant relationship between the dental caries and PTB, it is still important for the health professionals to promote oral health among the pregnant women. This is because pregnant women are susceptible to dental problems; have very limited knowledge and awareness about the importance of oral health and its potential impact on pregnancy outcomes [38, 42]. Furthermore, the risk of transmitting the oral cariogenic flora from the mother to her infant through feeding practices and predisposing the infant to early childhood caries in the future should not be neglected[43-46]. Therefore, large prospective studies aiming at ascertaining the association between dental caries and spontaneous PTB, according to the gestational age at occurrence, severity of the disease and presence of other co-morbidities are needed in order to elucidate the role, if any, of dental caries in increasing the risk of PTB.

REFERNCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
2. Slattery MM, Morrison JJ. Preterm delivery. Lancet. 2002;360(9344):1489–97.
3. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med. 1985;312(2):82–90.
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-9.
5. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG. 2006;113(Suppl 3):S17-42.
6. Jeffcoat MK, Geurs NC, Reddy MS, Goldenberg RL, Hauth JC. Current evidence regarding periodontal disease as a risk factor in preterm birth. Ann Periodontol. 2001;6:183–88.
7. Offenbacher S. Maternal periodontal infections, prematurity, and growth restriction. Clin Obstet Gynecol. 2004;47:808–21.
8. Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol. 2006;107(1):29–36.
9. Jarjoura K, Devine PC, Perez-Delboy A, Herrera-Abreu M, D'Alton M, Papapanou PN. Markers of periodontal infection and preterm birth. Am J Obstet Gynecol. 2005;192:513–19.
10. Goepfert AR, Jeffcoat MK, Andrews WW, Faye-Petersen O, Cliver SP, Goldenberg RL, et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol. 2004;104(4):777–83.
11. Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG. 2006;113:135–43.
12. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007;369(9555):51-9.
13. Martinez-Beneyto Y, Vera-Delgado MV, Perez, L, Maurandi A. Self-reported oral health and hygiene habits, dental decay, and periodontal condition among pregnant European women. Inl J Gynecol Obstet. 2011;114(1):18-22.
14. Gajendra S, Kumar JV. Oral health and pregnancy: a review. N Y State Dent J. 2004;70(1):40-44.
15. Silk H, Douglass AB, Douglass JM, Silk L. Oral health during pregnancy. Am Fam Physician. 2008;77(8):1139-44.
16. Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ. Salivary Actinimyces naeslundii genospecies 2 and Lactobacillus casei level predicts pregnancy outcome. J Periodontol. 2005;76(2):171-77.
17. Durand R, Gunselman EL, Hodges JS, DiAngelis AS, Michalowicz BS. A pilot study of the association of cariogenic bacteria and preterm birth. Oral Dis. 2009;15(6):400-06.
18. Meurman JH, Furuholm J, Kaaja R, Rintamaki H, Tikkanen U. Oral health in women with pregnancy and delivery complications. Clin Oral Investig. 2006;10(2):96-101.

19. Mumghamba EG, Manji KP. Maternal oral health status and preterm low birth weight at Muhimbili National Hospital, Tanzania: a case-control study. BMC Oral Health. 2007;7:8.
20. Heimonen A, Rintamaki H, Furuholm J, Janket SJ, Kaaja R, Meurman JH. Postpartum oral health parameters in women with preterm birth. Acta Odontol Scand. 2008;66(6):334-41.
21. Ryalat S, Sawair F, Baqain Z, Barghout N, Amin W, Badran D, Badran E. Effect of Oral Diseases on Mothers Giving Birth to Preterm Infants. Med Princ Pract. 2011;20(6):556-61.
22. Vergnes JN, Kaminski M, Lelong N, Musset AM, Sixou M, Nabet C, EPIPAP Group. Maternal dental caries and pre-term birth: results from the EPIPAP study. Acta Odontol Scand. 2011;69(4):248-56.
23. Acharya S, Pentapati KC, Bhat PV. Dental neglect and adverse birth outcomes: a validation and observational study. Int J Dent Hyg. 2013;11(2):91-8.
24. Harjunmaa U, Jarnstedt J, Alho L, Dewey KG, Cheung YB, Deitchler M, Ashorn U, Maleta K, Klein NJ, Ashorn P. Association between maternal dental periapical infections and pregnancy outcomes: results from a cross-sectional study in Malawi. 2015;20(11): 1549-58.
25. Saraiva MCP, Bettiol H, Barbieri MA, Silva AA. Are intrauterine growth restriction and preterm birth associated with dental caries? Community Dent Oral Epidemiol. 2007;35(5):364-76.
26. Abati S, Villa A, Cetin I, Dessole S, Luglie PF, Strohmenger L, Ottolonghi L, Campus GG. Lack of association between maternal periodontal status and adverse pregnancy outcomes: a multicentric epidemiologic study. J Matern Fetal Neonatal Med. 2013;26(4):369-72.
27. Buduneli N, Baylas H, Buduneli E, Turkoglu O, Kose T, Dahlen G. Periodontal infections and pre-term low birth weight: a case control study. J Clin Periodontol. 2005;32(2): 174-81.
28. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton) 2010;15(6):617–24.
29. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK). 2009.
30. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
31. World Health Organization. Preterm birth. 2017 [online] Available at http://www.who.int/mediacentre/factsheets/fs363/en/ [Accessed 3 May 2017].
32. World Health Organization. Oral health surveys: basic methods. 4th ed. 1997 Geneva.
33. Malmo University. Caries prevalence and Calculation. 2010 [online] Available at https://www.mah.se/CAPP/Methods-and-Indices/for-Caries-prevalence/ [Accessed 11 April 2017]
34. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. [Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 3 May 2017]

35. Achtari MD, Georgakopoulou EA, Afentoulide N. Dental care throughout pregnancy: what a dentists must know. Oral Health Dent Manag. 2012;11(4):169-76.
36. Huebner CE, Milgrom P, Conrad, D. et al. Providing dental care to pregnant patients: a survey of Oregon general dentists. J Am Dent Assoc. 2009;140(2):211-22.
37. Boggess KA, Urlaub DM, Massey KE, Moos MK, Matheson MB, Lorenz C. Oral hygiene practice and dental service utilization among pregnant women. J Am Dent Assoc. 2010;141(5): 553-61.
38. Hulla E, Turok Y, Nauta M, Yoong W. Self-reported oral hygiene habits, dental attendance and attitudes to dentistry during pregnancy in a sample of immigrant women in North London. Arch Gynecol Obstet. 2008;277(5):405-09.
39. Merglova V, Hecova H, Stehlikova J, Chaloupka P (2012) Oral health status of women with high-risk pregnancies. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2012; 156(4):337-41.
40. Shamsi M, Hidarnia A, Niknami S, Khorsandi M. The status of dental caries and some acting factors in a sample of Iranian women with pregnancy. World J Med Sci. 2013;9(4):190-97.
41. Kloetzel MK, Huebner CE, Milgrom P. Referrals for dental care during pregnancy. J Midwifery Womens Health. 2011;56(2):110-17.
42. Keirse MJ, Plutzer K. Women's attitudes to and perceptions of oral health and dental care during pregnancy. J Perinat Med. 2010;38(1):3-8.
43. Zanata RL, Navarro MF, Pereira JC, Franco EB, Lauris JR, Barbosa SH. Effect of caries preventive measures directed to expectant mothers on caries experience in their children. Braz Dent J. 2003;14(2):75-81.
44. Goldie MP. Oral health care for pregnant and postpartum women. Int J Dent Hyg. 2003;1(3):174-6.
45. Boggess KA, Edelstein BL. Oral health in women during preconception and pregnancy: implications for birth outcomes and infant oral health. Matern Child Health J. 2006;10 (5 Suppl):S169-74.
46. Boggess KA, Society for Maternal-Fetal Medicine Publications Committee. Maternal oral health in pregnancy. Obstet Gynecol. 2008;111(4):976-86.

TABLES

Table 1. General characteristics of the included studies.

Author	Year	Country	Period analyzed (y)	Study design	Gestational age at dental examination	Number of subject (n)	Definition of PTB
Martinez-Martinez	2016	Mexico	2013-2014	Retrospective	From the first trimester of pregnancy until 8 weeks postpartum	70	<37 weeks
Harjunmaa	2015	Malawi	2011-2013	Prospective	Within 6 weeks after delivery	1024	<37 weeks
Acharya	2013	India	2009	Retrospective	Within 1 day after delivery	316	<37 weeks
Vergnes	2011	France	2003-2006	Retrospective	Within 2–4 days post-partum	2201	<37 weeks
Ryalat	2011	Jordan	2009	Prospective	Within 1 week post-partum	200	<37 weeks
Durand	2009	France	2005-2006	Prospective	Within 8 weeks after delivery	107	<37 weeks
Heimonen	2008	Finland	2002-2004	Retrospective	Within 2 days post-partum	328	<37 weeks
Mumghamba	2007	Tanzania	NS	Retrospective	Within 40 days from delivery	373	<37 weeks
Meurman	2006	Finland	1998-2000	Retrospective	From the first trimester of pregnancy	207	<37 weeks

1. Martinez-Martinez RE, Moreno-Castillo DF, Loyola-Rodriguez JP, Sanchez-Medrano AG, Miguel-Hernandez JH, Olvera-Delgado JH, Dominguez-Perez RA. Association between periodontitis, periodontopathogens and preterm birth: is it real? Arch Gynecol Obstet. 2016;294(1):47-54
2. Harjunmaa U, Jarnstedt J, Alho L, Dewey KG, Cheung YB, Deitchler M, Ashorn U, Maleta K, Klein NJ, Ashorn P. Association between maternal dental periapical infections and pregnancy outcomes: results from a cross-sectional study in Malawi. 2015;20(11):1549-58.
3. Acharya S, Pentapati KC, Bhat PV. Dental neglect and adverse birth outcomes: a validation and observational study. Int J Dent Hyg. 2013;11(2):91-8.
4. Vergnes JN, Kaminski M, Lelong N, Musset AM, Sixou M, Nabet C, EPIPAP Group. Maternal dental caries and pre-term birth: results from the EPIPAP study. Acta Odontol Scand. 2011;69(4):248-56.
5. Ryalat S, Sawair F, Baqain Z, Barghout N, Amin W, Badran D, Badran E. Effect of Oral Diseases on Mothers Giving Birth to Preterm Infants. Med Princ Pract. 2011;20(6):556-61.
6. Durand R, Gunselman EL, Hodges JS, Diangelis AJ, Michalowicz BS. A pilot study of the association between cariogenic oral bacteria and preterm birth. Oral Dis. 2009;15(6):400-6.
7. Heimonen A, Rintamaki H, Furuholm J, Janket SJ, Kaaja R, Meurman JH. Postpartum oral health parameters in women with preterm birth. Acta Odontol Scand. 2008;66(6):334-41.
8. Mumghamba EG, Manji KP. Maternal oral health status and preterm low birth weight at Muhimbili National Hospital, Tanzania: a case-control study. BMC Oral Health. 2007;7:8
9. Meurman JH, Furuholm J, Kaaja R, Rintamaki H, Tikkanen U. Oral health in women with pregnancy and delivery complications. Clin Oral Investig. 2006;10(2):96-101.

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Martinez-Martinez	2016	★★	★	★
Harjunmaa	2015	★★	★	★
Acharya	2013	★★	★	★★
Vergnes	2011	★★★	★★	★
Ryalat	2011	★★★	★	★★
Durand	2009	★★★	★★	★★
Heimonen	2008	★★	★	★
Mumghamba	2007	★★	★	★
Meurman	2006	★★	★	★

Table 3. Selected outcomes evaluating the association between dental caries and preterm birth.

Outcomes	**N. studies (n/N)**	**Odds Ratio (95% CI)**	**p**	**I^2, %[a]**
Preterm birth (PTB), women with dental caries versus controls	5 (1472/4246)	1.16 (0.90; 1.49)	0.25	35
	N. studies (n/N)	**Mean difference (95% CI)**	**p**	**I^2, %**
DMFT (PTB versus Non-PTB)	5 (2963)	1.56 (-0.28; 3.41)	0.10	92
DMFS (PTB versus Non-PTB)	3 (2594)	-0.15 (-3.40; 3.09)	0.9	89

CI: Confidence interval. n: number of events. N: total number of participants. DMFT: Decayed, missed, and filled teeth. DMFS: Decayed, missed, and filled surface.
a: I^2 is a measure of the heterogeneity among the included studies. a value ≥50% indicates high while <50% low heterogeneity.

FUNDING

No funding was received for the conduction of this review.

The publication charges for this article have been funded by a grant from the publication fund of UiT The Arctic University of Norway.

CONTRIBUTORS

Study concept, design and methodology - MW, GA, FD'A, ER

Data Collection and entry - ER

Abstracts and articles review - MW, FD'A

Analysis and interpretation of data - F'DA, MW, GO, LM

Supervision - FD'A, GA, PB, TAT

Writing, review, critique, comments and revision of manuscript- MW, FD'A, ER, TAT, PB, GO, LM, GA

ACKNOWLEDGEMENT

We would sincerely like to thank Prof. S Acharya, Prof. S Abati, Prof. I Cetin, Prof. GG Campus, Prof. A Villa, Prof. R Martinez, Prof. S Ryalat, Prof. JH Meurman, Prof. Y Khader, Prof. A Heimonen, Prof. U Harjunmaa, Prof. R Durand, Prof. N Buduneli and Prof. AP Dasanayake for their co-operation and contribution by providing additional data and necessary information for this systemic review.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data is available.

ABBREVIATION

CI – Confidence Interval

DMFS – Decayed, Missing, Filled Surface

DMFT- Decayed, Missing, Filled Teeth

NOS - Newcastle-Ottawa Scale

OR – Odds Ratio

PTB – Preterm Birth

FIGURES

Figure_1. Systematic review flowchart

Figure_2. Pooled odd ratio (OR) for the risk of preterm birth (PTB) in women compared with those without dental caries.

Figure_3_a_b. Mean differences in DMFT and DMFS indices in women with dental caries compared to those who did not experience PTB.

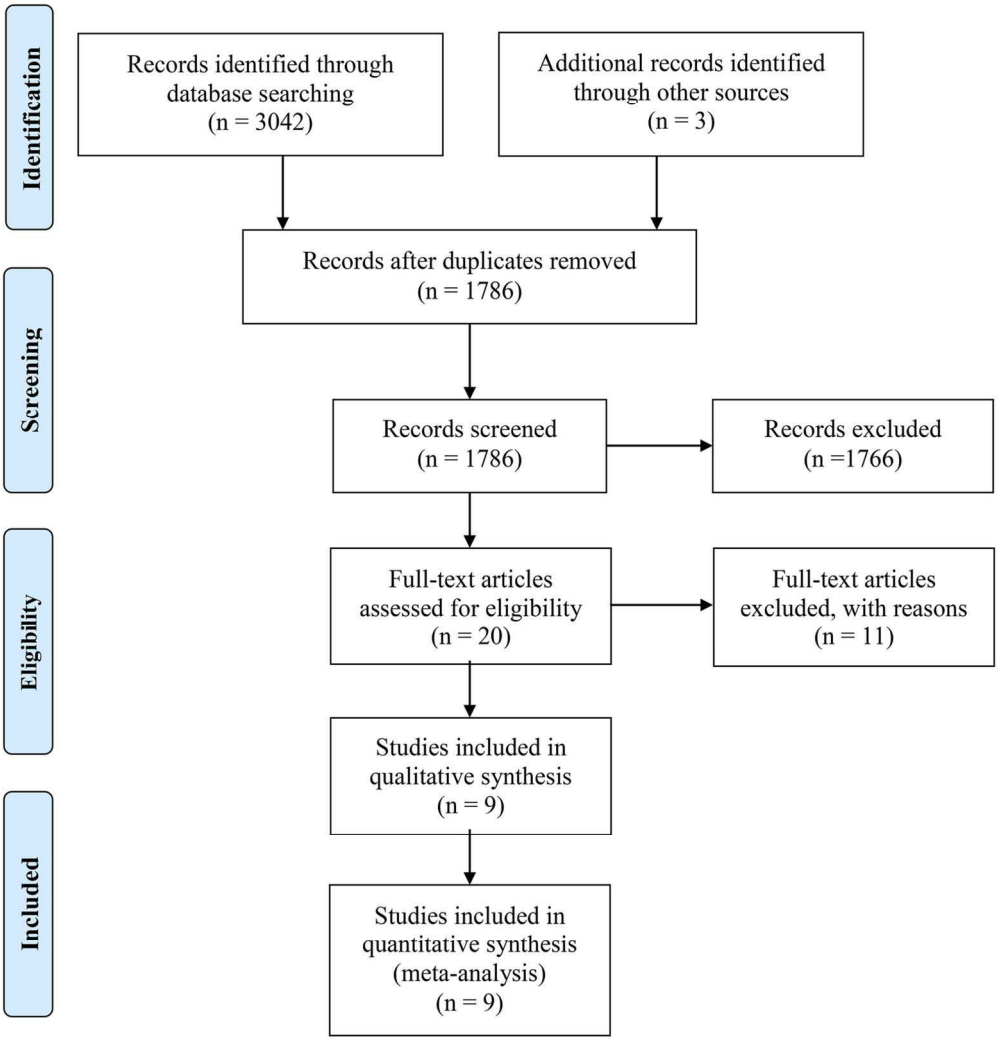


Figure_1. Systematic review flowchart

130x136mm (300 x 300 DPI)

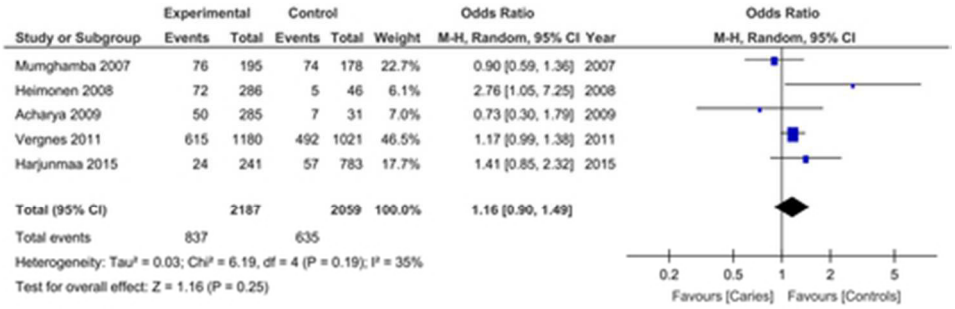


Figure_2. Pooled odd ratio (OR) for the risk of preterm birth (PTB) in women compared with those without dental caries.

40x12mm (300 x 300 DPI)

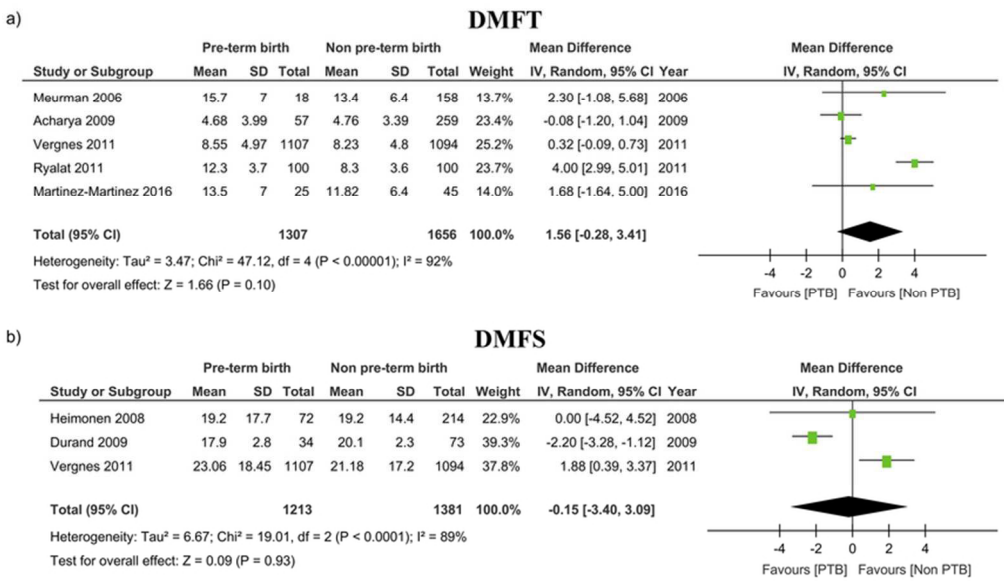
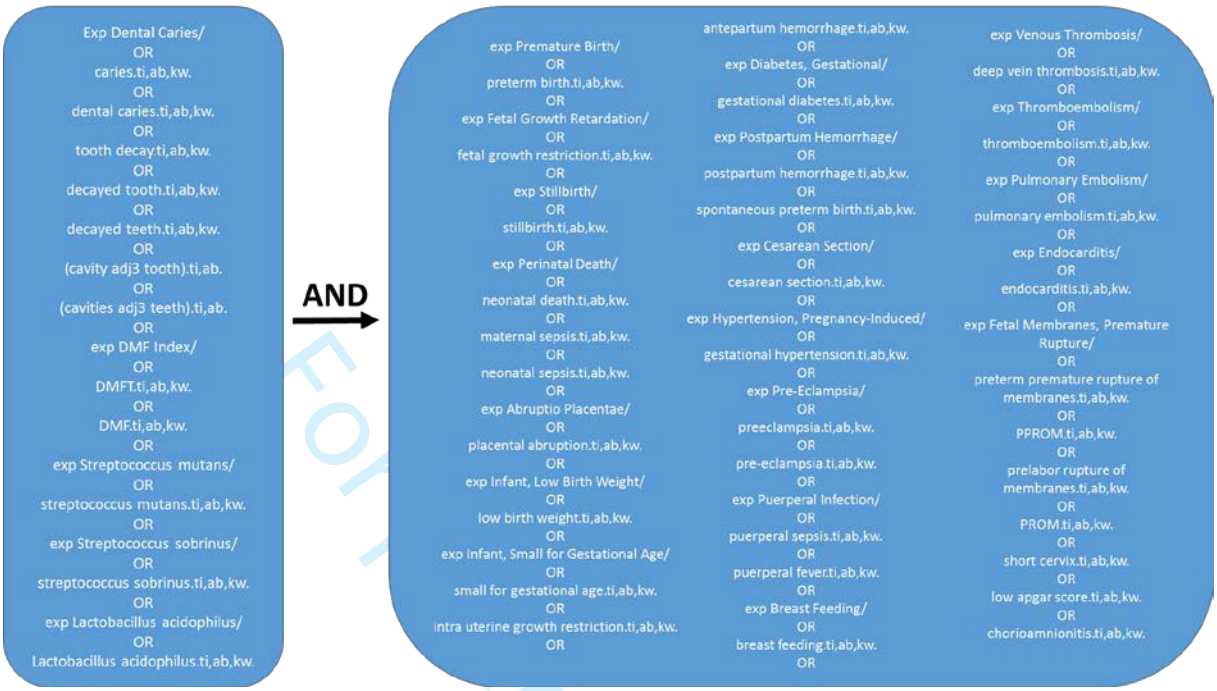


Figure_3_a_b. Mean differences in DMFT and DMFS indices in women with dental caries compared to those who did not experience PTB.

72x41mm (300 x 300 DPI)

Supplementary material 1



NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Supplementary Table 3. Excluded studies and reason for the exclusion.

Author	Year	Title	Reason for the exclusion
Buduneli	2005	Periodontal infections and pre-term low birth weight: a case-control study	The number of decayed teeth were provided as a continuous variable; thus it was not possible to extrapolate any data regarding the occurrence of PTB in women with compared to those without caries. Furthermore, no information on the DMFT score was provided by the authors.
Dasanayake	2005	Salivary Actinomyces naeslundii Genospecies 2 and Lactobacillus casei Levels Predict Pregnancy Outcomes	No data on the outcomes explored in this systematic review
Shulman	2005	Is There an Association between Low Birth Weight and Caries in the Primary Dentition?	No data on caries in pregnancy
Bosnjak	2006	Pre-term delivery and periodontal disease: a case–control study from Croatia	No data on the outcomes explored in this systematic review
Khader	2007	Risk Indicators of Pre-Eclampsia in North Jordan: Is Dental Caries Involved?	No data on caries and PTB
Saraiva	2007	Are intrauterine growth restriction and preterm birth associated with dental caries?	No data on caries in pregnancy
Cunha-Cruz	2009	Intrauterine Growth Restriction and Preterm Birth Were not Associated with Primary Teeth Caries	No data on caries in pregnancy
Durand	2009	A pilot study of the association between cariogenic oral bacteria and preterm birth	It was not possible to extrapolate data regarding the occurrence of PTB in pregnancies with compared to those without caries; furthermore, it was not possible to extract any information regarding the mean DMFT values in women who compared to those who did not deliver preterm
Merglova	2012	Oral health status of women with high-risk pregnancies	No data on the outcomes explored in this systematic review
Abati	2013	Lack of association between maternal periodontal status and adverse pregnancy outcomes: a multicentric epidemiologic study	It was not possible to extrapolate data regarding the occurrence of PTB in pregnancies with compared to those without caries; furthermore, it was not possible to extract any information regarding the mean DMFT values in women who compared to those who did
Sayyed	2014	The relationship between term pre-eclampsia and the risk of early childhood caries	No data on caries in pregnancy

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.