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Prenatal Oral Health Care and Early Childhood Caries Prevention: A Systematic Review and Meta-analysis

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Abstract

Despite the advancement of early childhood caries (ECC) prediction and treatment, ECC remains a significant public health burden in need of more effective preventive strategies. Pregnancy is an ideal period to promote ECC prevention given the profound influence of maternal oral health and behaviors on children's oral health. However, studies have shown debatable results with respect to the effectiveness of ECC prevention by means of prenatal intervention. Therefore, this study systematically reviewed the scientific evidence relating to the association between prenatal oral health care, ECC incidence and *Streptococcus mutans* carriage in children. Five studies (3 randomized control trials, 1 prospective cohort study and 1 nested case-control study) were included for qualitative assessment. Tested prenatal oral health care included providing fluoride supplements, oral examinations/cleanings, oral health education, dental treatment referrals and Xylitol gum chewing. Four studies that assessed ECC incidence reduction were included in meta-analysis using an unconditional generalized linear mixed effects model with random study effects and age as a covariate. The estimated odds ratio and 95% confidence intervals suggested a protective effect of prenatal oral health care against ECC onset before 4 years of age, 0.12 (0.02, 0.77) at 1 year of age, 0.18 (0.05, 0.63) at 2 years of age, 0.25 (0.09, 0.64) at 3 years of age, and 0.35 (0.12, 1.00) at 4 years of age. Children's *S. mutans* carriage was also significantly reduced in the intervention group. Future studies should consider testing strategies that restore an expectant mother's oral health to a disease-free state during pregnancy.

Keywords

Prenatal oral health care; Odds ratio; Caries; ECC; Child dentistry; Clinical studies; Risk factor

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Declaration of interests

The authors declare no conflict of interests.

Introduction

Although largely preventable, early childhood caries (ECC) remains the most common chronic childhood disease, with nearly 1.8 billion new cases per year globally [Disease et al., 2017; Dye et al., 2012; Dye et al., 2007], It afflicts approximately 37% of children aged 2-5 years in the US [Dye et al., 2012; Dye et al., 2007] and up to 73% of socioeconomically disadvantaged preschool children in both developing and industrialized countries [Dye et al., 2015]. ECC is defined as the presence of ≥1 decayed, missing (due to caries), or filled tooth surfaces in primary teeth in a child 71 months of age or younger [Colak et al., 2013]. Severe ECC (S-ECC) occurs in children <3 years of age with ≥1 decayed, missing (due to caries), or filled tooth surfaces and in children 4-6 years of age with elevated caries scores [Colak et al., 2013]. The short-term consequences of untreated ECC include pain, hospitalization and emergency room visits due to abscess and systemic infection, and even death [American Academy of Pediatric Dentistry Council on Clinical, 2005; Casamassimo et al., 2009]. Once decay has reached this stage, children often require total oral rehabilitation (TOR) under general anesthesia [Koo and Bowen, 2014] with multiple tooth extractions and restorations/crowns, at a cost of nearly $7000 per child (2009-2011 data in US) [Rashewsky et al., 2012]. In the long term, there is strong evidence that children who experienced ECC are much more likely to have diminished oral health-related quality of life and higher risk of caries lesions in permanent teeth [Heller et al., 2000; Powell, 1998].

Despite the advancement of ECC prediction and treatment strategies, ECC remains a public health burden. In the US; more than 1.5 billion dollars per year is spent on treatment. However, children remain at high risk for recurrent caries even after extensive TOR treatment. Up to 40% of children treated for S-ECC experience recurrent disease by the 6-month checkup post TOR[Berkowitz et al., 2011; Graves et al., 2004], despite pharmacologic interventions, such as topical fluoride/antimicrobial applications and dietary counseling to alter caries-promoting eating behaviors [Li and Tanner, 2015; O'Sullivan and Tinanoff, 1996]. Hence, more effective preventive strategies are critically needed.

Pregnancy is an ideal time to promote primary prevention of ECC in children given the profound influence of maternal health and behaviors on children's oral health outcomes [Iida, 2017], ECC is a multifactorial bacterial disease with *Streptococcus mutans* as the prime cariogenic bacterium, and strongly influenced by diet [Caufield et al., 1993; Kanasi et al., 2010; Klein et al., 2004; Klinke et al., 2014; Li et al., 2005; Slayton, 2011; Zhan et al., 2012]. Studies have shown that maternal untreated caries and greater level of salivary *S. mutans* increase the risk of ECC in children. Children's dietary and oral hygiene behaviors rely on parents or caregivers' oral health knowledge, beliefs and behaviors [Finlayson et al., 2007; Wigen et al., 2011]. While revisiting the children's dental caries risk model described by Fisher-Owens [Fisher-Owens et al., 2007] that included different levels of environmental elements, several factors that could potentially be influenced by mothers (underlined in red in Fig.1) including: 1) microflora and diet in the oral health element positioning at the oral health circle, 2) Health behaviors and practices, biological and genetic endowment, physical and demographic attributes, use of dental care, health behaviors and practices, and dental insurance, that are included in the child-level influences element; 3) family position, socioeconomic status physical safety, health status of parents, family function, culture and

health behaviors, practices, and coping skills of family, that lie in the family-level influences element. These factors in the aforementioned dental caries risk prediction model further emphasize the maternal role in ECC development. Thus, in theory, oral health care intervention during pregnancy presents an ideal entry point to preventing ECC.

Previously, studies have shown a positive ECC prevention outcome by providing prenatal oral health education or intervention [Gunay et al., 1998; Nakai et al., 2010]; however, another study failed to show more effective ECC prevention when intervention during pregnancy was compared to the control group. Therefore, the aim of this study is to systematically review the scientific evidence relating to the association between prenatal oral health care, reduced carriage of *S. mutans* and ECC prevention.

Methods

Search strategy

Database searches were conducted in May 2018, to identify published studies on prenatal oral health care and ECC related outcome (onset of ECC and/or oral *S. mutans* colonization). A medical reference librarian developed individual search strategies and retrieved citations from PubMed, Embase, Scopus, Web of Science, LILACS, Cochrane Library, and ClinicalTrials.gov. A combination of text words and controlled vocabulary terms were used (Prenatal Care, Oral Health, Child, Infant, Breast Feeding, Newborn, Dental Caries). A detailed search strategy is shown in the Appendix 1.

Inclusion/Exclusion criteria

This systematic review included case-control studies, retrospective or prospective cohort studies, randomized or non-randomized controlled trials that examined the effect of oral health care during pregnancy on the incidence of ECC and/or oral carriage of *S. mutans* in children under the age of 6. Two trained independent reviewers completed the article selection in accordance with the inclusion/exclusion criteria. The agreement between reviewers was satisfactory (K=0.81). Disagreement were resolved by consensus between the two reviewers.

The following inclusion and exclusion criteria were used for literature selection.

Inclusion criteria:

Types of participants

- Pregnant women and their children under the age of 6

Types of intervention(s)/phenomena of interest

- Prenatal oral health care utilization/intervention

Types of comparisons

- Pregnant women who received and did not receive prenatal oral health care

Types of outcomes

- Reduced dental caries in children
- Reduced oral carriage of *S. mutans*

Types of studies

- Case-control studies
- Retrospective or prospective cohort studies
- Randomized and non-randomized controlled trials

Types of statistical data

- Odds ratios (OR)
- Relative risk (RR)
- Confidence intervals (CI)
- p-values
- Frequency of an absolute number of events vs. total number of individuals per group

Exclusion criteria:

- *In vitro* studies
- Animal studies
- Papers with abstract only
- Literature reviews
- Letters to the editor
- Editorials
- Patient hand outs
- Case report or case series
- Cross-sectional studies

Data extraction

Descriptive data, including clinical and methodological factors such as country of origin, study design, study site, dental examination, dental examiner calibration, age of subjects, type of prenatal oral health care intervention, outcome measures (ECC and/or oral *S. mutans*), as well as results from statistical analyses were obtained using an extraction form (Appendix 2).

Qualitative assessment and quantitative analysis

The quality of the selected articles were assessed using two methodological validities: 1) Cochrane Collaboration's tool for assessing risk of bias in randomized trials [Higgins et al., 2011]. Articles were scaled for the following bias categories: selection bias, performance

bias, detection bias, attrition bias, reporting bias and other bias. 2) Adapted Down and Black scoring [Downs and Black, 1998] that assess the methodological quality of both randomized and non-randomized studies of health care interventions. A total score of 26 represents the highest study quality.

For the articles selected for quantitative analysis, R package metaphor was used for meta-analysis (https://cran.r-project.org/web/packages/metafor/). The OR and 95% CI and p-values were estimated using an unconditional generalized linear mixed effects model with random study effects. Children's age at study endpoint was used as a covariate. Heterogeneity among the studies was evaluated using I^2 statistics and tested using likelihood ratio test. A forest plot was created to summarize the meta-analysis study results.

Results

The literature analyses identified a total of 5,881 papers from the database search (Fig. 2). A total of 1,855 duplicate references were removed. The remaining 4026 studies were imported into an Endnote Library for further review. From those, 3854 studies were excluded after title screening, 128 studies were excluded after abstract screening. The remaining 44 articles were selected for a full text review. After the full text analysis, 40 studies were eliminated based on the exclusion criteria and 5 articles were chosen for qualitative assessment. For the quantitative assessment using meta-analysis to assess the effect of prenatal oral health care intervention on the onset of ECC, four out of 5 articles that received qualitative assessment were included. One article that was removed from meta-analysis only included oral *S. mutans* carriage in children, but not ECC as the outcome [Nakai et al., 2010]. The full list of excluded articles after full text review is shown in Appendix 3.

Study characteristics

The characteristics of studies included in the qualitative review are summarized in Table 1. All five studies were published between 1997-2016. One was conducted in the US [Leverett et al., 1997], one in Germany [Gunay et al., 1998] and one in Australia [Plutzer and Spencer, 2008], Two were conducted in Japan[Nakai et al., 2016; Nakai et al., 2010]. Among the 5 studies, three were randomized control trials [Leverett et al., 1997; Nakai et al., 2010; Plutzer and Spencer, 2008], one was a prospective cohort study [Gunay et al., 1998] and 1 was a nested case-control in a cohort study [Nakai et al., 2016]. Oral health care intervention adopted in all qualitative studies extended the intervention period from the prenatal to infant stage. The interventions included: a) Fluoride-based intervention, where fluoride supplement intake was provided to pregnant women and their infant in a population that was not exposed to optimal water fluoridation [Leverett et al., 1997]; b) Primary-Primary prevention originally proposed by Axelsson [Axelsson, 1988], where all prophylactic measures were carried out in pregnant women in order to prevent the transmission of cariogenic bacteria and improve feeding behaviors after birth [Gunay et al., 1998]; c) Oral health education promotion in pregnant women, which was used in Plutzer's study [Plutzer and Spencer, 2008] and in Nakai's study [Nakai et al., 2016], It was called antenatal health care in

Nakai's study; d) Xylitol gum chewing in pregnant women [Nakai et al., 2010]. Intervention approaches are further detailed in Table 1.

Study outcomes were assessed when children reached 2-5 years of age. The onset of ECC and salivary *S. mutans* carriage are the two primary outcomes evaluated in these 5 studies. Quality and risk of bias for all 5 studies was assessed and shown in Fig. 3. Two studies with randomized controlled trial design have high quality based on Cochrane risk of bias assessment tool [Higgins et al., 2011] and Down and Black scoring system [Downs and Black, 1998], the other 3 studies have moderate quality.

Prenatal oral health care and ECC prevention

Three studies [Gunay et al., 1998; Nakai et al., 2016; Plutzer and Spencer, 2008] revealed lower ECC incidence in the group that received oral health care intervention during pregnancy and early infancy, when compared to the control group. Prenatal oral health care intervention approaches used in these 3 studies were Primary-Primary prevention, oral examination and cleaning, and oral health education. One study [Leverett et al., 1997] investigating fluoride supplement use during pregnancy showed no statistical difference ($p>0.05$) in caries incidence in children between the intervention (8%) and control group (9%).

Meta-analysis was performed on four studies that assessed ECC incidence (results shown in Fig. 4). In particular, Gunay et al [Gunay et al., 1998] examined the same cohort of children at two time points, when they reached 3- and 4-years of age; their results were included as two data sets in the meta-analysis. Study heterogeneity ($I^2=75.06\%$) and the related p-value were calculated using likelihood ratio test ($p<0.0001$).

The empirical ORs and 95% CIs of the studies included in meta-analysis are shown in Fig. 4A. When compared to the control group, the empirical odds ratio (95% CI) of ECC in children whose mothers received Primary-Primary prevention is 0.04 (0.00, 0.68) at 3 years of age [Gunay et al., 1998] and 0.13 (0.04, 0.42) at 4 years of age [Gunay et al., 1998]. Compared to the control group, the empirical odds ratio (95% CI) of ECC is 0.17 (0.06, 0.49) in children whose mothers received oral health education [Plutzer and Spencer, 2008], 0.36 (0.15, 0.85) in children whose mothers received antenatal health care [Nakai et al., 2016], and 0.94 (0.57, 1.56) in children whose mothers received a fluoride supplement [Leverett et al., 1997].

Based on the generalized linear mixed effect model with covariate age, the estimates of ORs and 95% CIs indicate that regarding ECC incidence, there is a statistically significant difference between the intervention and control groups for children younger than 4 years old, regardless of intervention modalities (detailed in Fig 4B). The odds of experiencing ECC among the children younger than 4 whose mothers received prenatal oral health care is significantly less than those children in the control group, indicating a protective effect of prenatal oral health care against ECC development with 95% confidence intervals whose upper bounds smaller than 1. For instance, the estimated odds ratios (95% CI) are 0.12 (0.02, 0.77) for children at 1 year of age, 0.18 (0.05, 0.63) for children of 2 years of age, 0.25 (0.09, 0.64) at 3 years of age, and 0.35 (0.12, 1.00) at 4 years of age, respectively. For

children 5 years of age or older, the estimated odds ratio is still smaller than 1, but the 95% confidence interval contains 1, indicating the protective effect becomes insignificant.

Prenatal oral health care and reduction of *S. mutans* carriage in children

The effect of prenatal oral health care intervention on the reduction of children's *S. mutans* carriage was assessed in two studies [Gunay et al., 1998; Nakai et al., 2010], In the study by Günay et al [Gunay et al., 1998], *S. mutans* reduction was significant between the intervention and control groups; 100% of children in the intervention group remained *S. mutans* free by the age of 3, whereas only 38.5% of children in the control group remained *S. mutans* free by the age of 3. Moreover, mothers in the intervention group also showed a significant improvement in plaque index and reduction in *S. mutans* score. The study by Nakai et al [Nakai et al., 2010] showed that significantly more children in the xylitol chewing group remained *S. mutans* free at 9-, 12- and 24-months. Furthermore, pre- and perinatal xylitol chewing by mothers delayed *S. mutans* carriage in children. The children's *S. mutans* acquisition age in the xylitol chewing group was 8.8 months later than that of the control group (Mean age, 20.8 *vs.* 12.0 months).

Discussion

The results of this review have shown a reduced ECC incidence in children whose mothers received prenatal oral health care. ECC is a multifactorial disease with complex socioeconomic, genetic, oral hygiene behaviors, bacterial and diet factors that affect risk for this disease [Ruby and Goldner, 2007; Wang et al., 2012]. *S. mutans* and, more recently, *Candida* species have been implicated as potential major etiological microorganisms that may be involved in the initiation and development of ECC [Gross et al., 2012; Tanzer et al., 2001; Xiao et al., 2018]. Studies have shown an association between maternal poor oral health and increased risk for ECC [Chaffee et al., 2014]. The association between mother's and child's oral health could possibly be explained by: 1) mothers' oral health behavior, e.g. perception and knowledge influences the dental health of their children [Goettems et al., 2012; Olak et al., 2018; Saied-Moallemi et al., 2008]; 2) mother might be a main source of her children's acquisition of oral *S. mutans* and *Candida sp.* [Bliss et al., 2008; Caufield et al., 2005; Childers et al., 2017; Waggoner-Fountain et al., 1996; Xiao et al., 2016].

The following points should be considered when interpreting the results of this review: 1) various intervention modalities and frequencies were used across the 5 studies, which produced challenges for data analysis, e.g., the heterogeneity of studies included in the meta-analysis is significant ($p<0.01$). 2) The timing of the main outcome measurement (ECC incidence) with respect to children's age lacks consistency throughout the 5 studies. The peak of ECC onset is 3 years of age; there is a significant increase in incidence between age 2 and 3. Kopycka [Kopycka-Kedzierawski et al., 2008] reported a 26% ECC prevalence among 2 years olds in Rochester, NY; Quinonez [Quinonez et al., 2001] reported a 20% ECC prevalence in children 18-36 months of age in North Carolina, US; Rosenblatt [Rosenblatt and Zarzar, 2002] reported a 46% S-ECC prevalence rate among Brazilian children 25-36 months of age. Two studies included in the quantitative analysis only monitored study children until age 2, which might have underestimated the preventive effect

of prenatal oral health care on ECC. 3) As we were not able to collect study subjects' data on other caries determinants, e.g. demographic, socioeconomic, sugar consumption, etc., the meta-analysis performed in this review did not use multivariate analyses to consider potential confounders mentioned above. Given the multifactorial nature of ECC, the ORs calculated might have under- or overestimated the effectiveness of prenatal oral health care. 4) For the strategies that used prenatal oral health education or Primary-Primary prevention, it was not clear to what degree the prenatal oral intervention had improved or restored pregnant women's oral health. Therefore, it is challenging to make recommendations on how much oral health care a pregnant woman needs to receive and how much oral health education is needed to demonstrate effective ECC prevention in children. Taking the aforementioned limitations into account, future randomized clinical trials are desired to test prenatal oral health care strategies that maintain or restore an expectant mother's oral health and that measure improvements in oral health knowledge.

Moreover, another dilemma that needs to be considered is that: although routine oral care during pregnancy has been demonstrated to be safe, and recommendations for prenatal oral care have been disseminated globally, utilization of prenatal oral health care is limited in both developed and developing countries [Rocha et al., 2018]. In contrast to the limited utilization of prenatal dental care, over 76% of US women admitted to suffering from oral health problems (pain, bleeding gums and oral infection) during pregnancy while more than 43% did not have a dental checkup during pregnancy [Editorial, 2015]. Furthermore, dental care utilization during pregnancy was lower among black women [Thompson et al., 2013], ethnic minorities [Marchi et al., 2010] and women with socioeconomic disadvantages [Singhal et al., 2014]. Thus, oral health represents an important often-neglected heath disparity during pregnancy among minority women and women with socioeconomic disadvantages [Azofeifa et al., 2014; Guamizo-Herreno and Wehby, 2012]. In order to use successfully prenatal oral health care to prevent ECC, future efforts need to gain a better understanding of the factors that enable or inhibit the use of prenatal dental care at both the community and individual levels. Effective strategies might derive from collaborations among dental and medical providers involved in women's and children's dental and medical health, policy makers and community social workers.

Conclusions

This review reports a reduced ECC incidence and *S. mutans* carriage in children whose mothers received prenatal oral health care. Maintaining oral health and improving oral health care knowledge during pregnancy is a critical and promising step towards ECC prevention. Future studies should consider testing strategies that maintains an expectant mother's oral health or restores an expectant mother's oral health to a disease free state during pregnancy.

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JX contributed to the study design, JX, NA, DAC, TTW performed the data acquisition and analysis. JX, DAC, DTK, RJB, LR, HM, EE and YR contributed to the data interpretation, manuscript writing and critical revision of the manuscript.

Appendix 1:: Search strategy

PubMed Strategy

("Oral Health"[Mesh] OR "Oral Hygiene"[Mesh] OR "Dental Health Services"[Mesh] OR "Dental Care"[Mesh] OR (Oral Health) OR (Oral Hygiene) OR (Dental Health Services) OR (Dental Care) OR (Dental Health) OR (Dental Hygiene) OR (Dental Procedure) OR (Mouth Hygiene) OR (Tooth Hygiene) OR (Teeth Hygiene) OR (Oral Care) OR (Tooth Care) OR (Teeth Care) OR (Mouth Care)) **AND** ("Prenatal Care"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR (Prenatal Care) OR Pregnancy OR (Pregnant Women) OR Prenatal OR Antenatal OR Gestation OR Pregnant) **AND** ("Dental Caries"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature"[Mesh] OR "Fetal Death"[Mesh] OR "Attitude to Health"[Mesh] OR "Health Behavior"[Mesh] OR "Health Education, Dental"[Mesh] OR Caries OR (Tooth Decay) OR (Teeth Decay) OR (Dental Decay) OR (Dental Fissure) OR (Dental Fissures) OR (Tooth Fissure) OR (Tooth Fissures) OR (Teeth Fissure) OR (Teeth Fissures) OR (Carious Dentin) OR (Carious Dentine) OR (White Spot) OR (White Spots) OR Cavity OR Cavities OR (Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Prematuritas OR Preterm OR (Pre Term) OR (Fetus Death) OR (Fetus Death) OR (Fetus Deaths) OR (Fetus Demise) OR (Fetus Mummification) OR (Fetus Resorption) OR (Fetus Resorptions) OR (Fetal Deaths) OR (Fetal Demise) OR (Fetal Mummification) OR (Fetal Resorption) OR (Fetal Resorptions) OR Stillbirth OR Stillbirths OR Stillborn OR (Health Attitude) OR (Health Attitudes) OR (Health Knowledge) OR (Health Behavior) OR (Health Behaviors) OR (Health Behaviour) OR (Health Behaviours) OR (Health Education)) **AND** (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))

Embase Strategy

('Mouth Hygiene'/exp OR 'Dental Procedure'/exp OR 'Dental health'/exp OR (Oral Health) OR (Oral Hygiene) OR (Dental Health Services) OR (Dental Care) OR (Dental Health) OR (Dental Hygiene) OR (Dental Procedure) OR (Mouth Hygiene) OR (Tooth Hygiene) OR (Teeth Hygiene) OR (Oral Care) OR (Tooth Care) OR (Teeth Care) OR (Mouth Care)) **AND** ('Prenatal Care'/exp OR 'Pregnancy'/exp OR 'Pregnant Woman'/exp OR (Prenatal Care) OR Pregnancy OR (Pregnant Women) OR Prenatal OR Antenatal OR Gestation OR Pregnant) **AND** ('Dental Caries'/exp OR 'Low Birth Weight'/exp OR 'Prematurity'/exp OR 'Fetus Death'/exp OR 'Attitude to Health'/exp OR 'Health Behavior'/exp OR 'Dental Health Education'/exp OR Caries OR (Tooth Decay) OR (Teeth Decay) OR (Dental Decay) OR (Dental Fissure) OR (Dental Fissures) OR (Tooth Fissure) OR (Tooth Fissures) OR (Teeth Fissure) OR (Teeth Fissures) OR (Carious Dentin) OR (Carious Dentine) OR (White Spot) OR (White Spots) OR Cavity OR Cavities OR (Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Prematuritas OR Preterm OR (Pre Term)

OR (Fetus Death) OR (Fetus Death) OR (Fetus Deaths) OR (Fetus Demise) OR (Fetus Mummification) OR (Fetus Resorption) OR (Fetus Resorptions) OR (Fetal Death) OR (Fetal Deaths) OR (Fetal Demise) OR (Fetal Mummification) OR (Fetal Resorption) OR (Fetal Resorptions) OR Stillbirth OR Stillbirths OR Stillborn OR (Health Attitude) OR (Health Attitudes) OR (Health Knowledge) OR (Health Behavior) OR (Health Behaviors) OR (Health Behaviour) OR (Health Behaviours) OR (Health Education)) **AND** ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti)

Web of Science Strategy

((Oral Health) OR (Oral Hygiene) OR (Dental Health Services) OR (Dental Care) OR (Dental Health) OR (Dental Hygiene) OR (Dental Procedure) OR (Mouth Hygiene) OR (Tooth Hygiene) OR (Teeth Hygiene) OR (Oral Care) OR (Tooth Care) OR (Teeth Care) OR (Mouth Care)) **AND** ((Prenatal Care) OR Pregnancy OR (Pregnant Women) OR Prenatal OR Antenatal OR Gestation OR Pregnant) **AND** (Caries OR (Tooth Decay) OR (Teeth Decay) OR (Dental Decay) OR (Dental Fissure) OR (Dental Fissures) OR (Tooth Fissure) OR (Tooth Fissures) OR (Teeth Fissure) OR (Teeth Fissures) OR (Carious Dentin) OR (Carious Dentine) OR (White Spot) OR (White Spots) OR Cavity OR Cavities OR (Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Prematuritas OR Preterm OR (Pre Term) OR (Fetus Death) OR (Fetus Death) OR (Fetus Deaths) OR (Fetus Demise) OR (Fetus Mummification) OR (Fetus Resorption) OR (Fetus Resorptions) OR (Fetal Death) OR (Fetal Deaths) OR (Fetal Demise) OR (Fetal Mummification) OR (Fetal Resorption) OR (Fetal Resorptions) OR Stillbirth OR Stillbirths OR Stillborn OR (Health Attitude) OR (Health Attitudes) OR (Health Knowledge) OR (Health Behavior) OR (Health Behaviors) OR (Health Behaviour) OR (Health Behaviours) OR (Health Education)) **AND** (random* OR factorial* OR crossover* OR (cross over*) OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*)

LILACS Database Strategy

((Oral Health) OR (Oral Hygiene) OR (Dental Health Services) OR (Dental Care) OR (Dental Health) OR (Dental Hygiene) OR (Dental Procedure) OR (Mouth Hygiene) OR (Tooth Hygiene) OR (Teeth Hygiene) OR (Oral Care) OR (Tooth Care) OR (Teeth Care) OR (Mouth Care)) **AND** ((Prenatal Care) OR Pregnancy OR (Pregnant Women) OR Prenatal OR Antenatal OR Gestation OR Pregnant) **AND** (Caries OR (Tooth Decay) OR (Teeth Decay) OR (Dental Decay) OR (Dental Fissure) OR (Dental Fissures) OR (Tooth Fissure) OR (Tooth Fissures) OR (Teeth Fissure) OR (Teeth Fissures) OR (Carious Dentin) OR (Carious Dentine) OR (White Spot) OR (White Spots) OR Cavity OR Cavities OR (Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Prematuritas OR Preterm OR (Pre Term) OR (Fetus Death) OR (Fetus Death) OR (Fetus Deaths) OR (Fetus Demise) OR (Fetus Mummification) OR (Fetus Resorption) OR (Fetus Resorptions) OR (Fetal Death) OR (Fetal Deaths) OR (Fetal Demise) OR (Fetal Mummification) OR (Fetal Resorption) OR (Fetal Resorptions) OR Stillbirth OR Stillbirths OR Stillborn OR

(Health Attitude) OR (Health Attitudes) OR (Health Knowledge) OR (Health Behavior) OR (Health Behaviors) OR (Health Behaviour) OR (Health Behaviours) OR (Health Education)) **AND** (random* OR factorial* OR crossover* OR (cross over*) OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*)

Cochrane Database Strategy

((Oral Health) OR (Oral Hygiene) OR (Dental Health Services) OR (Dental Care) OR (Dental Health) OR (Dental Hygiene) OR (Dental Procedure) OR (Mouth Hygiene) OR (Tooth Hygiene) OR (Teeth Hygiene) OR (Oral Care) OR (Tooth Care) OR (Teeth Care) OR (Mouth Care)) **AND** ((Prenatal Care) OR Pregnancy OR (Pregnant Women) OR Prenatal OR Antenatal OR Gestation OR Pregnant) **AND** (Caries OR (Tooth Decay) OR (Teeth Decay) OR (Dental Decay) OR (Dental Fissure) OR (Dental Fissures) OR (Tooth Fissure) OR (Tooth Fissures) OR (Teeth Fissure) OR (Teeth Fissures) OR (Carious Dentin) OR (Carious Dentine) OR (White Spot) OR (White Spots) OR Cavity OR Cavities OR (Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Prematuritas OR Preterm OR (Pre Term) OR (Fetus Death) OR (Fetus Death) OR (Fetus Deaths) OR (Fetus Demise) OR (Fetus Mummification) OR (Fetus Resorption) OR (Fetus Resorptions) OR (Fetal Death) OR (Fetal Deaths) OR (Fetal Demise) OR (Fetal Mummification) OR (Fetal Resorption) OR (Fetal Resorptions) OR Stillbirth OR Stillbirths OR Stillborn OR (Health Attitude) OR (Health Attitudes) OR (Health Knowledge) OR (Health Behavior) OR (Health Behaviors) OR (Health Behaviour) OR (Health Behaviours) OR (Health Education)) **AND** (random* OR factorial* OR crossover* OR (cross over*) OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*)

ClinicalTrials.gov Strategy

((Oral OR Dental OR Mouth OR Touth OR Teeth) AND (Health OR Hygiene OR Care OR Procedure)) **AND** (Pregnancy OR Pregnant OR Prenatal OR Antenatal OR Gestation) **AND** (Caries OR Carious OR ((Tooth OR Teeth OR Dental) AND (Decay OR Fissure*)) OR (White Spot*) OR Cavit*) / ((Low Birth Weight) OR Underweight OR Premature OR (Pre Mature) OR Prematurity OR Preterm OR (Pre Term) OR ((Fetus OR Fetal) AND (Death* OR Demise OR Mummification OR Resorption*)) OR Stillbirth* OR Stillborn) / ((Health Attitude*) OR (Health Knowledge) OR (Health Behavior*) OR (Health Behaviour*) OR (Health Education))

Appendix 2:: Data extraction form

Reviewer: _____ **Date:** _____
Study ID: _____
Title: _____
Lead author (First and Corresponding): _____
Publication year: _____ **Country:** _____ **language:** _____
Journal: _____
Aim of the study: _____

Part I: Study Methods

Design:

- ☐ Randomized clinical trial
- ☐ Non-randomized clinical trial
- ☐ other (describe)_____

Origin of the study:
City_____ **State/Province**_____ **Country:**_____

Subject recruitment site:

- ☐ Hospital/Dental School clinic
- ☐ Community
- ☐ Epidemiology Study site
- ☐ Other (describe) _____

Study visits: _____ ☐ Didn't specify

Study duration: _____ ☐ Didn't specify

How many examiners? _____

Examiner Intra and inter-Calibration? _____

Part II: Subject Information

Subject age: _____

Number of subjects: _____

Subject race (number/percentage if applicable):

- ☐ Caucasian _____
- ☐ African American _____
- ☐ Asian _____
- ☐ Others (describe) _____

Subject medical background:

- ☐ Healthy
- ☐ non-healthy (specify disease) _____

Part III: Oral Health Care Delivery Method

Caries clinical examination method:

- ☐ Visual-tactile examination
- ☐ Radiograph
- ☐ Others (describe) _____

Caries recording system:

- ☐ *dmft/s*
- ☐ ICDAS
- ☐ Others (describe) _____

Types of prenatal oral care

- ☐ Visual-tactile examination
- ☐ Cleaning
- ☐ Oral health education
- ☐ Others (describe) _____

Who delivered prenatal oral care?

- ☐ Dentist
- ☐ Hygienist
- ☐ Social worker
- ☐ OB doctor
- ☐ Primary health care physician
- ☐ Midwife
- ☐ Others (describe) _____

Part IV: Any oral sample collected? If yes, proceed with the following:

Sample source (If applicable):

☐ Saliva: ☐ Non-stimulated ☐ Stimulated ☐ Didn't specify

☐ Plaque: ☐ Supragingival ☐ Subgingival ☐ mixed ☐ Sound surface ☐ Carious lesion

☐ Swab

☐ others (describe) _____

Bacteria isolation and identification method:

☐ Culture (Describe type of plate agar) _____

☐ PCR

☐ others (describe) _____

Examined bacteria type:

☐ *S. mutans* ☐ *Lactobacillus* ☐ others (describe) _____

Part V: Results

- Improved oral health knowledge: ☐ Yes ☐ No
- Improved oral health during pregnancy: ☐ Yes ☐ No
- Reduced dental caries in children: ☐ Yes ☐ No
- Reduced *Streptococcus mutans* carriage ☐ Yes ☐ No

Part VI: Statistical analysis results (if applicable)

☐ **Statistical analysis type: _____**

Author's conclusion:

_____

_____

Reviewer's comments:

_____

_____

Appendix 3:: Excluded articles after full-text review

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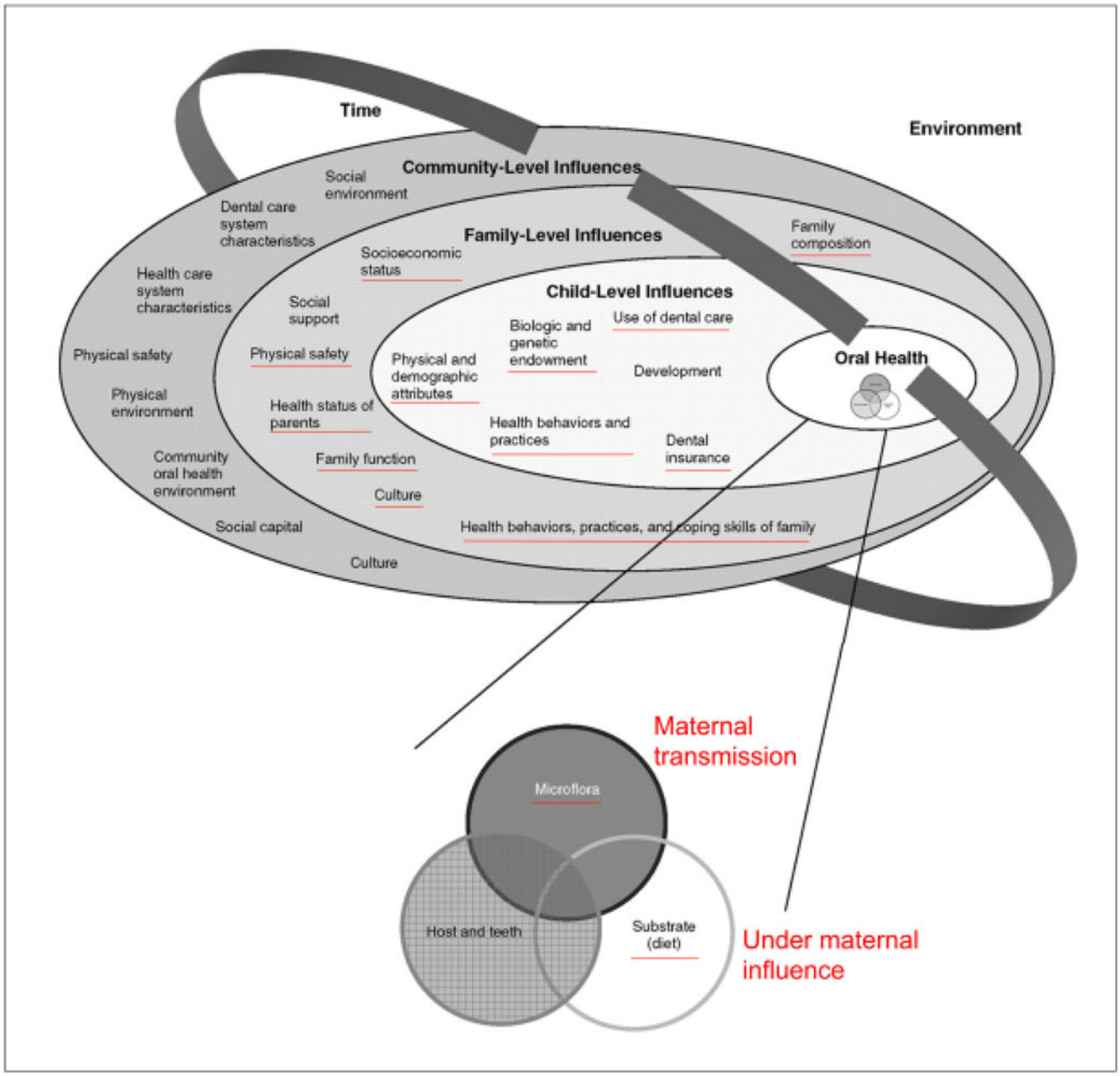


Figure 1. Modified Fisher-Owens conceptual model of child, family, and community influences on oral health outcomes of children.

Factors underlined in red are those that could potentially be influenced by maternal attributes.

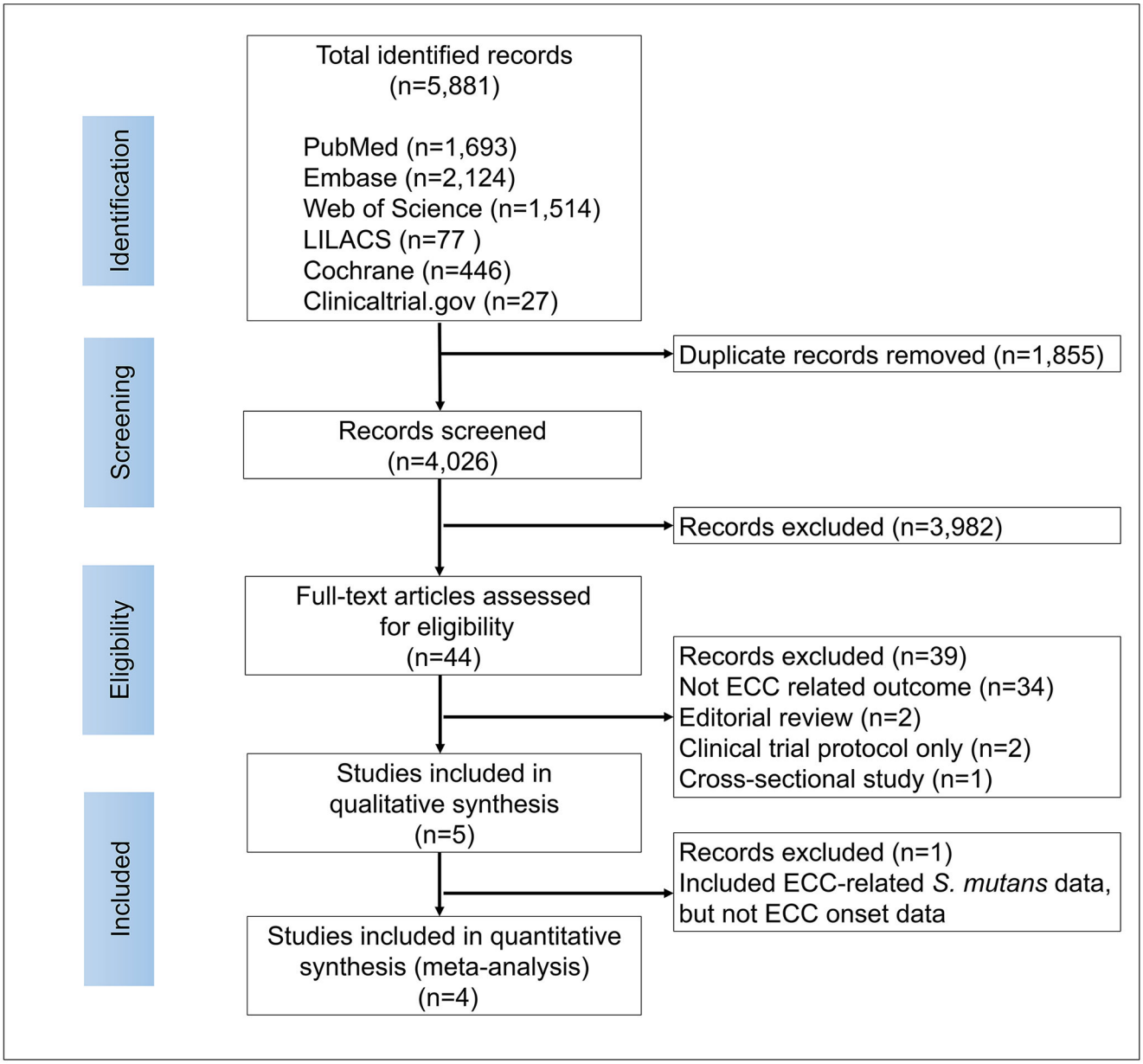


Figure 2. Flow diagram of study identification.

The four-phase Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to determine the number of studies identified, screened, eligible, and included in the systematic review and meta-analysis (http://www.prisma-statement.org).

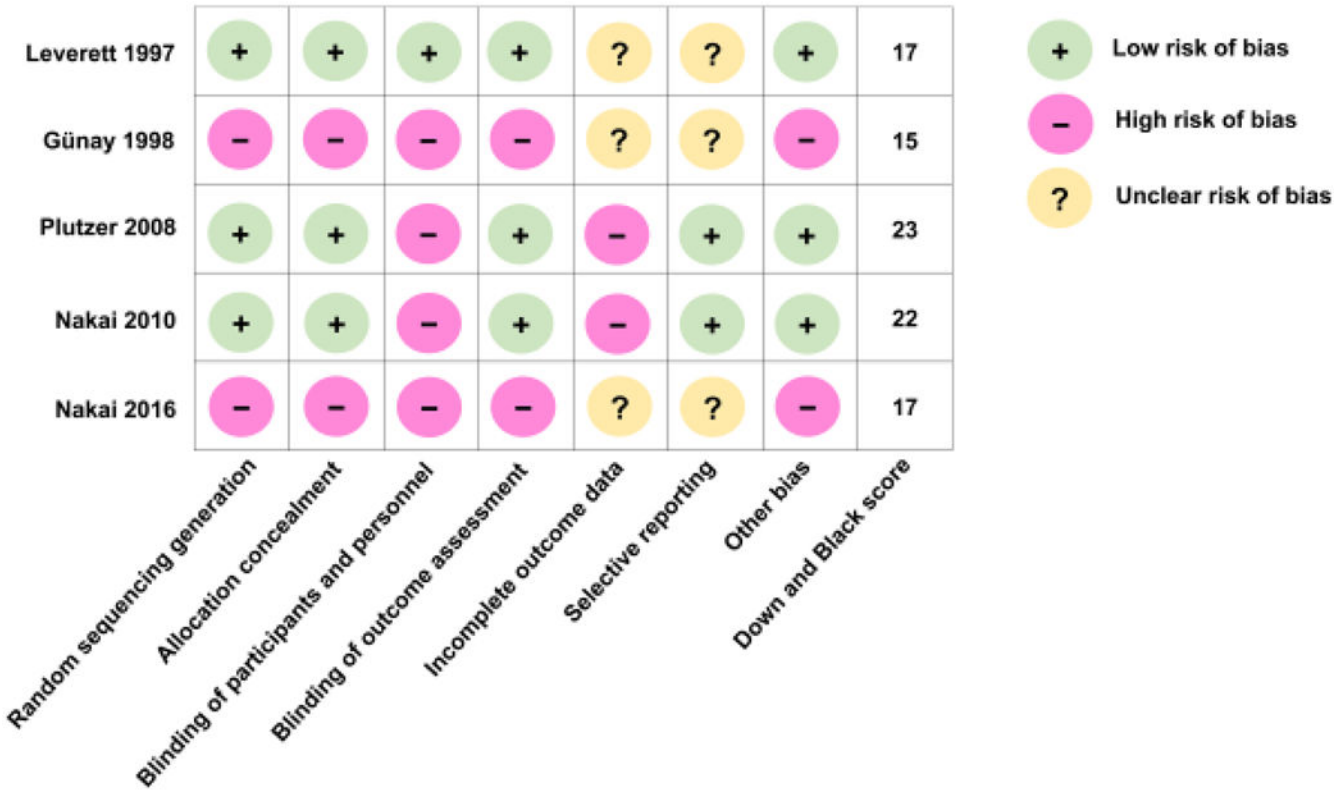


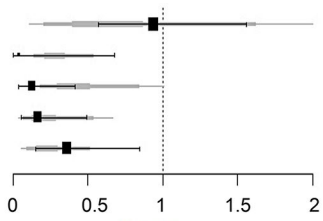
Figure 3. Summary of quality and risk of bias assessment using Cochrane Collaboration's tool for assessing risk of bias in randomized trials and adapted Down and Black scoring tool.

The quality of the selected articles were assessed using two methodological validities: 1) Cochrane Collaboration's tool for assessing risk of bias in randomized trials [Higgins et al., 2011]. 2) Adapted Down and Black scoring [Downs and Black, 1998] that assess the methodological quality of both randomized and non-randomized studies of health care interventions. A total score of 26 represents the highest study quality.

(A)

Studies (child age at the exam)	Empirical odds ratio (95% CI)	ECC /Intervention	ECC/Control
Leverett 1997 (5 years old)	0.94 (0.57, 1.56)	32/398	34/400
Günay 1998 (3 years old)	0.04 (0.00, 0.68)	0/54	12/65
Günay 1998 (4 years old)	0.13 (0.04, 0.42)	4/47	19/45
Plutzer 2008 (1.67 years old)	0.17 (0.06, 0.49)	4/232	20/209
Nakai 2016 (2.1 years old)	0.36 (0.15, 0.85)	57/125	21/30

I^2 (p<0.01)



(B) Estimated odds ratio of experiencing ECC in children whose mothers received prenatal oral health care intervention vs. children in control group

Child age (year)	Odds ratio (95% CI)
1	0.12 (0.02, 0.77)
2	0.18 (0.05, 0.63)
3	0.25 (0.09, 0.64)
4	0.35 (0.12, 1.00)
5	0.49 (0.11, 2.24)

Figure 4. Odds Ratio of ECC events in prenatal oral health care intervention group and control group.

Meta-analysis was performed on four studies that assessed ECC incidence. In particular, Günay et al, 1998 examined the same cohort of children at two time points, when they reached 3- and 4- years of age; their results were included as two data sets in the meta-analysis. Study heterogeneity (I^2=75.06%) and the related p-value were calculated using likelihood ratio test (p<0.0001). The empirical odds ratio (OR) and 95% confidence interval (CI) of each study included in the meta-analysis was shown in (A). Based on the generalized linear mixed effect model with covariate age, the estimates of OR and 95% CI shown in (B) indicate that regarding ECC incidence, there is a statistically significant difference between the intervention and control groups for children younger than 4 years of age. The solid line indicates when OR=1.

Table 1.

Characteristics of studies included in qualitative assessment

Author Year	City, country, study design	Study site	Child age at exam	Total subjects	Intervention	Control
Leverett 1997	Maine, US, RCT	Private Obstetric practice and hospital prenatal clinics	5 years	Subjects lived in an area without water fluoridation. **Intervention:** 585 pregnant women at baseline 398 children at 5 years **Control:** 590 pregnant women (baseline) 400 children at 5 years	**-Mother:** daily intake of tablet contains 1 mg fluoride beginning with the 4th month of pregnancy until the end of pregnancy (approximately 6 mons). **-Infant:** daily drop of fluoride water from birth to 2 years of age. 0.5mg tablet from 2-3 years of age.	No fluoride intake
Günay 1998	Gennany, Prospective cohort study	Medical University of Hannover (Intervention group); Various kindergartens (control group)	3 years and 4 years	**Intervention:** 86 pregnant women; 54 mother-child dyads (3 years of age) 47 mother-child dyads (4 years of age) **Control:** 65 children (3 years of age) 45 children (4 years of age)	**-Primary-Primary prevention** -Pregnancy 1stvisit: •Dental examination findings •Individual preventive self-care oral hygiene instruction (OHI) •Instruction on avoid microbes transmission •Caries etiology education •Referral for dental treatment if needed Pregnancy 2nd visit (>8 mons gestational age) •Education about infection related to caries maternal-child transmission -After birth visit (0-3 years): •Mother-Child dyads: •Exam •OHI -After birth visit (3-4 years): •OHI	Children from various kindergartens who were not in the intervention group

Author Year	City, country, study design	Study site	Child age at exam	Total subjects	Intervention	Control
					•Cleaning •Topical fluoride and chlorhexidine varnish	
Plutzer 2008	Adelaide, Australia, RCT	Adelaide public hospital	20 ±2.5 mons	**Intervention:** 327 pregnant women; 232 children **Control:** 322 pregnant women; 209 children	-Oral health promotion information was given to mothers at a total of 3 rounds, 1 during pregnancy and 2 between 6–12 mons after birth -Two subgroups were included with additional structured telephone consultation 6–12 mons afterbirth in one subgroup.	Oral health promotion information was NOT given.
Nakai 2010	Okayama, Japan, RCT	Miyake obstetrics and Gynecology Clinic and Hello Dental Clinic	15 mons	**Intervention:** 56 pregnant women and 50 children examined at 6 mons, 46 children examined at 15 mons **Control:** 51 pregnant women and 35 children examined at 6 mons, 31 children examined at 15 mons	-At 6 mons pregnant: basic prevention measures (Oral examination, OHI, Cleaning) -From 6 mons pregnant to 9 mons after birth: Xylitol gum (each gum pellet contains 1.32 g xylitol) chewing 4 times/day ≥5min	At 6 mons pregnant: basic prevention measures (Oral examination, OHI, Cleaning)
Nakai 2016	Okayama, Japan, nested case control in a cohort study	Miyake obstetrics and Gynecology Clinic and Hello Dental Clinic	2.1±0.8 yrs	**Intervention:** 125 children **Control:** 30 children	-Antenatal health care (detail is not specified)	No antenatal health care

Author Year	Dental examination calibration	Outcome measurement	Statistical analysis	Study findings	Limitations
Leverett 1997	Not documented	• DMFS/dfs •Fluorosis using Dean criteria	Relative risk and 95% Confidence interval	-No statistical difference of caries incidence in children was seen between intervention (8%) and control group (9%). -There was no strong relationship between exposure to prenatal fluoride and fluorosis. -The tendency for deciduous maxillary second molars in females exposed to prenatal fluoride showed more fluorosis.	There is no other prenatal oral health care intervention other than fluoride supplement
Günay 1998	Not documented	• DMFS/*dmfs* • Proximal plaque index	*t*-test	-Caries and *S. mutans* reduction were significant between intervention and control groups	Referral was given to mothers who need dental

Author Year	Dental examination calibration	Outcome measurement	Statistical analysis	Study findings	Limitations
		• Salivary *S. mutans* (Dentocult SM)		**Children at age 3:** Intervention: • 0% caries (+) • 100% *S. mutans* score 0 Control: • 18.5% caries (+) with a 4.5 mean value of *dmfs*, • 38.5% *S. mutans* score 0 • 29.2% *S. mutans* score 1 • 20% *S. mutans* score 2 • 12.3% *S. mutans* score 3 **Children at age 4:** Intervention: • 8.5% caries (+) with a 1.5 mean value of *dmfs* • 42.6% *S. mutans* score 0 • 36.2% *S. mutans* score 1 • 19.1% *S. mutans* score 2 • 2.1% *S. mutans* score 3 Control: • 42.3% caries (+) with a 7.0 mean value of *dmfs* • 26.2% *S. mutans* score 0 • 13.3% *S. mutans* score 1 • 22.2% *S. mutans* score 2 • 37.7% *S. mutans* score 3 -Mothers showed a significant improvement in plaque index and reduction in *S. mutans* score	treatment, however Whether mothers received dental treatment was not noted. Whether pregnant women and their children in control group have received oral health care were unknown.
Plutzer 2008	Not documented	Incidence of S-ECC (AAPD definition)	Fisher's exact test	-Caries reduction was significant between intervention and control groups. • Intervention: S-ECC 1.7% • Control: S-ECC 9.6% -No difference between intervention subgroups with/without additional structured telephone consultation	Dental examiners were blinded, but the subjects were randomized into intervention or control group without blinding.
Nakai 2010	Intra-rate and inter-rate reliability tested. Kappa>0.80	Salivary *S. mutans* (Dentocult SM)	t-test, Chi-square and Fisher's exact tests	-Significantly more children in intervention group exhibited undetectable MS levels (score 0) on both the tongue and the gingival or tooth surfaces at 9, 12, and 24 mos. -The children in control group acquired *S. mutans* 8.8 mons earlier than those in intervention group (Mean, 12.0 vs. 20.8 mons)	Caries was not evaluated in children. Study did not use a control gum.
Nakai 2016	Not documented	*dmft*	Odds ratios and 95% confidence intervals	-Receiving antenatal health care (AOR, 3.27; 95% CI, 1.30-8.24) and child's having regular check-ups (AOR, 3.42; 95% CI, 1.35-8.69) were significantly associated with caries-free status among three-year old children.	The subjects in control group is much less than the intervention

*DMFS: Decayed, missing, filled surfaces in permanent dentition.

**dmft:* decayed, missing, filled teeth in primary dentition.

**S. mutans* scoring in Günay's study: 0=0-10^3 cfu (colony forming unit)/ml, 1=10^3-10^5 cfu/ml, 2=10^5-106 cfu/ml; 3= >10^6 cfu/ml.