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Systematic Review

Impact of Pharmacological Interventions in Expectant Mothers Resulting in Altered Mutans Streptococci Levels in Their Children

Murugan Satta Muthu, MDS, PhD[1] • Saikia Ankita, MDS[2] • Apathsakayan Renugalakshmi, MDS[3] • Kirubakaran Richard[4]

Abstract: ***Purpose:*** *The purpose of this systematic review was to assess whether prenatal use of fluoride, chlorhexidine mouthrinses, and xylitol could alter the mutans streptococci levels in children.* ***Methods:*** *A systematic search of clinical trials was implemented for the Cochrane Oral Health Group's Trials Register, PubMed, PMC, NCBI, ClinicalKey, Google Scholar, LILACS, and Science Direct. A search for ongoing trials was also undertaken in the clinicaltrial.gov database to identify eligible studies. Data regarding methodology, participants, types of interventions, and outcomes were extracted, and the risk of bias was also assessed independently by two review authors.* ***Results:*** *Only two clinical trials fulfilled the inclusion criteria. Although one study showed significant results, the overall result of this systematic review showed no statistical significance. A risk ratio and 95 percent confidence interval of 0.1 (0.01 to 1.89) were obtained.* ***Conclusions:*** *Statistically significant results were reported in both the included studies; however, systematic analysis revealed a dearth of current evidence to support the general recommendation of pharmacological interventions for expectant mothers resulting in altered mutans streptococci levels in their children. (Pediatr Dent 2015;37(5):) Received August 7, 2014 / Last Revision March 26, 2015 / Accepted March 27, 2015*

KEYWORDS: EARLY CHILDHOOD CARIES, PRENATAL, XYLITOL, FLUORIDE, SYSTEMATIC REVIEW

The term early childhood caries (**ECC**) was first suggested at a 1994 workshop, where an attempt was made to focus on multiple factors (i.e., behavioral, socioeconomic, and psychosocial) that contributed to dental caries at such early ages.[1,2] ECC is defined as "the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces" in any primary tooth in a child 71 months old or younger.[3] The two principal microorganisms responsible for the causation of ECC are *Streptococcus mutans* (**SM**) and *Streptococcus sobrinus*.[4] It has been well documented that the mutans streptococci (**MS**) colonization of an infant may occur as early as the time of birth[4.] Maternal transmission of MS to their children is also well established.[5]

Phenotypically and genotypically, SM levels in mothers and children have been shown to be similar.[6-9] MS found in ECC is predominantly acquired from the mother's saliva; thus, the caries risk of the infant is directly proportional to the bacterial load of the mother.[10] The maternal salivary bacterial load not only is associated with oral infection among children but also predicts a high risk of ECC occurrence.[11] A study by Li et al. reported that neonatal factors, such as mode of delivery, may also be potential risk factors for the early acquisition of MS via vertical transmission.[12] Therefore, a knowledge of various methods for the prenatal prevention of MS colonization is mandatory to suppress the maternal MS reservoirs, thus preventing or delaying the infant acquisition of MS.[10,12-14]

Pharmacological interventions, such as xylitol gums,[15,16] fluoride tablets, varnish, rinses,[16,17] and chlorhexidine mouthrinses/varnish[13,16,19] have been used during pregnancy to assess the possible reduction of caries incidence. Few studies[16] also compared the effects of three strategies: (1) biannual chlorhexidine treatments for mothers; (2) fluoride varnish treatments for mothers; or (3) maternal xylitol gum-chewing for children from three to 24 months old. In two-year-olds, the MS prevalences were 9.7 percent (xylitol), 28.6 percent (chlorhexidine), and 48.5 percent (fluoride).[16] Thorild et al. reported that maternal xylitol gum-chewing in six- to eight-month-olds significantly reduced MS transmission compared with the chewing of two control gums by the two control groups containing chlorhexidine/xylitol and sodium fluoride, with respective MS prevalences of 10 percent, 16 percent, and 28 percent. Leverett et al.[18] conducted a trial to test the caries-preventive efficacy of prenatal fluoride supplementation in 798 children followed until five years old but found no statistically significant difference in the study group with respect to caries in the primary dentition. Maturo et al. concluded that fluoride administration during pregnancy and postpartum had no significant impact on caries incidence. Prenatal administration of xylitol gums, fluoride (in tablet or rinse form), and chlorhexidine rinses have shown to reduce the transmission of MS in mothers to their offspring.[13,15,16,18-20]

Xylitol reduces MS levels in plaque and saliva. It acts by decreasing the synthesis of insoluble extracellular polysaccharides, thus reducing the risk of adhesion of MS to the enamel and, consequently, inhibiting MS transmission. It acts by disrupting the energy production processes of MS that lead to a futile energy consumption cycle and cell death.[20] Maternal MS reservoirs can also be suppressed by the use of chlorhexidine and/or fluoride.[21] The caries-preventive effect of topical fluoride is based on three main mechanisms: (1) promotion of remineralization; (2) inhibition of demineralization; and (3) interference with bacterial growth and metabolism.[22] Many authors have reported that the administration of fluoride during pregnancy is the first step toward caries prevention.[17,23]

For over 30 years, chlorhexidine has been studied as an antimicrobial agent for the chemical control of plaque and prevention of caries. It is a strong base and has a bacteriostatic

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effect at low concentrations. At higher concentrations, chlorhexidine acts as a bactericidal agent.[24-26] The use of maternal postpartum chlorhexidine regimen, combined with oral health counseling and preventive child fluoride varnish applications, did not, however, show a significant reduction in ECC.[27]

The prevalence of ECC among children from different regions and ethnic backgrounds has been documented. The etiology of ECC mainly involves bacterial, dietary, and host determinants that are influenced by the interplay of multiple sociological and environmental factors. Studies on the risk of ECC in different populations have reported various results, including an association between ECC and inappropriate feeding practices in very young children.[28-32] Even in developed countries like the United States, ECC is highly prevalent and increasing in poor and near-poor U.S. preschool children. This disease still remains largely untreated in children younger than three years old.[33,34]

The efficacy of postnatal interventions in expectant mothers for preventing dental caries and MS transmission in their children has been thoroughly studied[18]; however, data regarding the efficacy of prenatal interventions remain unclear. Therefore, the purpose of this paper was to provide a systematic review of the current literature assessing the efficacy of maternal administration of fluoride, chlorhexidine mouthrinses, and xylitol in altering the mutans streptococci levels in children.

Methods

Search strategy. For the identification of studies included or considered in this systematic review, detailed search strategies were developed for each database searched. The Cochrane Oral Health Group's Trials Register, PubMed, PMC, NCBI, ClinicalKey, Google Scholar, LILACS, and Science Direct were searched using MeSH terms and free-text words (Figure 1). search for ongoing trials was undertaken on the *clinicaltrial.gov* A database on November 25, 2013. Only trials published in the English language were included. There was no restriction regarding date of publication. All pediatric dentistry journals, including *International Journal of Pediatric Dentistry*, *Pediatric Dentistry*, *Journal of Clinical Pediatric Dentistry*, *Journal of Indian Society of Pedodontics and Preventive Dentistry*, *Journal of Dentistry for Children*, *European Archives of Pediatric Dentistry*, *European Journal of Paediatric Dentistry*, and issues of *Caries Research* published until August 2013, were hand searched independently by both review authors. The references of all eligible trials were checked for potential studies. Reference lists of articles were further scanned if they appeared eligible to the present review. One author was contacted regarding a potential study for a full-text article that was later excluded, since it did not meet the inclusion criteria of this review.

Inclusion criteria. Individual or quasi-randomized clinical trials were included if they evaluated the efficacy of one or more pharmacological interventions (xylitol, fluoride, and chlorhexidine mouthrinses) for expectant mothers to reduce the occurrence of ECC and alter mutans streptococci levels. Trials were included only if the outcome was measured by recording the average decayed, missing, and filled surfaces for permanent (DMFS) and primary (dmfs) teeth, mutans streptococci levels, or any other measures in the child and mother before and after interventions.

Exclusion criteria. Trials were excluded if interventions were given to both mother and child. Studies were excluded if participants were given treatment such as restorations during the intervention period.

Data collection and extraction. The titles and abstracts (when available) of all reports identified through the search

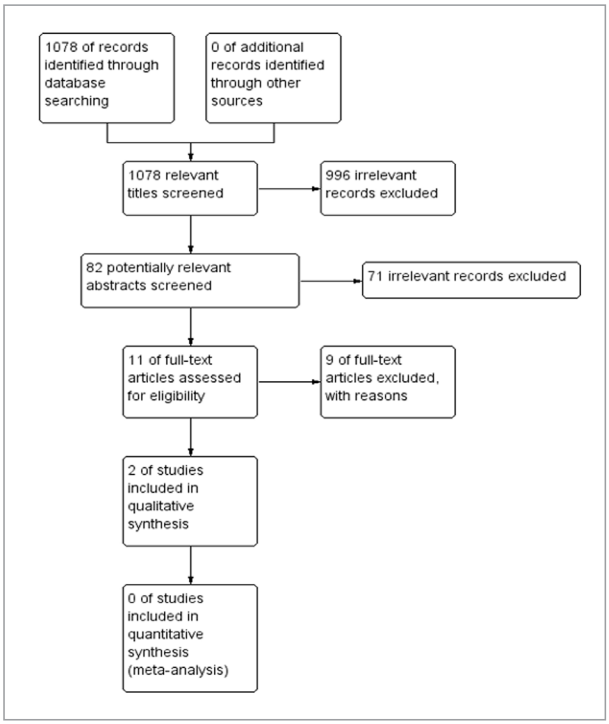

Figure 1. Electronic Search Strategy.

Search strings

 # 1 Search
("dental caries"[MeSH Terms] OR ("dental"[All Fields] AND "caries"[All Fields]) OR "dental caries"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("fluorides"[MeSH Terms] OR "fluorides"[All Fields] OR "fluoride"[All Fields]) OR ("chlorhexidine"[MeSH Terms] OR "chlorhexidine"[All Fields]) OR ("xylitol"[MeSH Terms] OR "xylitol"[All Fields]) AND intervention[All Fields] AND ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]) AND (("gravidity"[MeSH Terms] OR "gravidity"[All Fields] OR "pregnant"[All Fields]) AND ("mothers"[MeSH Terms] OR "mothers"[All Fields]))

#2 Search
("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("dental caries"[MeSH Terms] OR ("dental"[All Fields] AND "caries"[All Fields]) OR "dental caries"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) AND ("Intervention (Amstelveen)"[Journal] OR "intervention"[All Fields] OR "Interv Sch Clin"[Journal] OR "intervention"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND ("mothers"[MeSH Terms] OR "mothers"[All Fields])

#3 Search
children AND dental caries AND pregnancy AND intervention AND prevention

#4 Search
expectant mothers AND xylitol AND prevention AND dental caries

#5 Search
expectant mothers AND xylitol OR chlorhexidine OR fluoride AND intervention AND prevention AND dental caries AND children

Figure 2. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding, and including the studies found from the electronic search.

were independently scanned by two review authors and classified as relevant, irrelevant, or unclear. For all relevant and unclear studies, full reports were obtained. Two authors independently assessed all full-text articles to establish whether the trials selected met all inclusion criteria. Any disagreement was resolved by consensus after an independent co-author was consulted. Data were extracted from all the included studies.

Data analysis. Both authors independently used the Cochrane Collaboration's tool for assessing risk of bias in included studies.[35,36] The seven domains assessed were: (1) allocation concealment; (2) blinding of participants and personnel; (3) adequate sequence generation; (4) blinding of outcome assessors; (5) incomplete outcome data addressed; (6) selective outcome reporting; and (7) any other bias that may be present. A risk-of-bias table was completed for each included study, which recorded the judgment of the risk of bias for each domain in a study. Possible judgments were low risk of bias, high risk of bias, or unclear risk of bias.[35] Each study was analyzed separately by two review authors using a standardized risk-of-bias form, and the overall risk of bias of each

Table 1. OVERVIEW OF INCLUDED STUDIES

Author and year (reference)	Study design	No. of participants	No. analyzed	Type of intervention and dose	Time frame for study	Outcome measures	*P*-value
Nakai et al.[15] (2010)	RCT	Xylitol group (56) and control group (51)	Xylitol group (46) and control group (31)	Xylitol gums, 1.32 g, Lotte Co. Ltd. 1 gum pellet for ≥ 5 mins at least 4x/day	16 months; intervention was given at the end of the sixth month of pregnancy and terminated 13 months later	Salivary and plaque samples taken at 6, 9, 12, 18, and 24 mos old	<.001 (N=82)* (at 12 mos) .035 (N=77)* (at 24 mos)
Brambilla et al.[13] (1998)	RCT	Experimental (N=33) and control (N=32) groups	Experimental (N=31) and control (N=29) groups	Fluoride (0.05 percent) and chlorhexidine (0.12 percent) mouthrinse daily use in 3 cycles of 20 days with two 10-day rinse free intervals; control group=1 mg systemic fluoride starting at last week of sixth month of pregnancy	30 months; interventions were given at the end of the sixth month of pregnancy and continued until delivery	Salivary streptococci levels at 3 (baseline), 6, and 9 mos of pregnancy and 6, 12, 18, and 24 mos after delivery	<.001† (at 30 months)

* *P*-value calculated by Fisher's exact test. † *P*-value calculated by the Peto test and Peto's generalized Wilcoxon test.

Table 2. CHARACTERISTICS OF EXCLUDED STUDIES

Studies	Study design	Interventions	Time of intervention	Reason for exclusion
Alamoudi et al., 2012[30]	RCT	Xylitol gums + restorative treatment	After pregnancy	Interventions after pregnancy
Glenn et al., 1982[16]	Case control study	Fluoridated water + fluoride tablets	During pregnancy	Not RCT
Goldie et al., 2003[30]	Review	Chlorhexidine and xylitol	Pregnancy	Not RCT
Meyer et al., 2010[10]	Prospective clinical trial	Education about oral health care, dental treatment	During and after pregnancy	Different intervention types and times
Isokangas et al., 2000[31]	Case control study	Xylitol, fluoride, chlorhexidine	Pregnancy and postpartum	Not RCT; interventions were also given 24 mos after delivery
Kohler and Andréen, 2012[32]	Retrospective study	Systemic fluoride	During pregnancy	Not RCT
Leverett et al., 1997[33]	RCT	Mother: fluoride tablets Infant: fluoride drops	6th month of pregnancy	Interventions for both mother and child
Maturo et al., 2011[34]	Retrospective study	Fluoride	During pregnancy	Not RCT
Zanata et al., 2003[35]	Prospective study	Experimental group (mothers) = OHI + counseling + topical application of sodium fluoride and iodine solution after oral prophylaxis; control group (mothers) = OHI + counseling	From 6 mos of pregnancy to 12 mos after delivery	Not RCT; interventions given postpartum

study was decided after both the authors' judgments were discussed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for grading evidence.[37]

The data were analyzed with Review Manager (Review Manager 5.2) software (Cochrane Collaboration, Oxford, U.K.) following the advice suggested in chapter nine of the Cochrane Handbook of Systematic Reviews of Interventions 5.0.2.[36] All data were verified by both authors prior to being entered into the software for analysis. For dichotomous outcomes, the results were expressed as risk ratios with 95 percent confidence intervals. Heterogeneity was assessed by examination of the overlap of confidence intervals across the included studies in each forest plot. The chi-square test was used to assess whether observed differences in results were statistically significant at $P<.01$. Since this test is not sufficiently robust to assess heterogeneity because of the few studies included in the meta-analysis, I^2 statistics, which quantify the degree of true variation across the studies by percentage, were used. Fixed-effects models were also used throughout the analysis. In the event of a substantial amount of heterogeneity (greater than 50 percent), a random-effects model was used. Cluster-randomized controlled trials and crossover trials were not identified in our search results. Sensitivity analysis was undertaken to determine whether conclusions reached would be affected by per-protocol analysis versus intention-to-treat analysis. Subgroup analysis was not performed.

Results

From the electronic search strategy, as previously described, 1,078 reports were retrieved. No additional records were obtained after hand searches and searches for ongoing trials. After all duplicates were excluded and titles and abstracts were screened, 11 reports were identified as those that fulfilled the inclusion criteria. Full-text articles of these 11 reports were obtained for the assessment of potential eligibility. Two studies were finally included in this review. Details of all included studies are presented in Table 1. The two included trials were judged as having unclear risk of bias whenever there were insufficient data regarding allocation concealment and blinding, whereas high dropout rates posed a threat to the validity for one study. Baseline characteristics were similar in both the studies. Nine studies were excluded (see Table 2). A PRISMA flow chart (Figure 2) describes the selection process.

The first study reported on xylitol gum as the intervention and was conducted by Nakai et al.[15] The effect of maternal chewing of xylitol gum in reducing mother-child transmission of MS was assessed, and the xylitol-group children were less likely to show MS colonization than were those in the control group. Results of this study indicated that such interventions might prevent or delay mother-child MS transmission in a Japanese population. The risk ratio and 95 percent confidence interval of 0.1 (0.01 to 1.89) were obtained.

The second included study was conducted in San Paolo Hospital, Milan, Italy, in which 0.05 percent sodium fluoride and 0.12 percent chlorhexidine mouthrinses were used as interventions to reduce the MS load in children.[13] The results of the study by Brambilla et al.[13] did not provide sufficient data; all the means were smaller than the standard deviation in the experimental group, suggesting that this group's data were highly skewed, which prevented the calculation of a pooled weighted mean difference.[13] Thus, an overall grade could not be ascertained due to unclear risk of bias. Table 3 shows risk of assessment for both studies, while Table 4 shows a comparison of MS levels at baseline and at the ends of studies between the control and the experimental groups.

A meta-analysis was not possible since both the included trials compared different types of interventions. Also, a funnel plot to assess the publication bias could not be achieved because of the small number of studies included in the systematic review.

Discussion

A search of the literature revealed the administration of numerous maternal interventions for reducing the MS levels in children. However, there are fewer studies regarding the administration of pharmacological interventions confined to the prenatal period. Thus, the prime focus of this review was to assess the efficacy of pharmacological interventions on expectant mothers in altering the MS levels in children. To the best of our knowledge, this is the first systematic review that evaluates the effects of prenatal interventions on MS transmission from mother to child.

Table 3. RISK-OF-BIAS TABLE OF INCLUDED STUDIES

Bias	Author's judgment
Random sequence generation	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Low risk
Selective reporting (reporting bias)	Low risk
Others (potential risk of bias)	Unclear risk

Table 4. BASELINE AND FINAL MS LEVELS AND P-VALUES FOR THE DIFFERENCE IN MS LEVELS BETWEEN THE CONTROL AND EXPERIMENTAL GROUPS IN BOTH INCLUDED STUDIES

	Control group			Experimental group			
Study	N*	Baseline	Final	N	Baseline	Final	*P*-value
Nakai et al.[15] (2010)	31	32 (91.4)**	4 (12)**	46	50 (100)**	17 (37)**	$P=.035$†
Brambilla et al.[13] (1998)	29	583 (342)‡	621 (369)‡	31	660 (430)‡	17 (21)‡	$P<.001$§

* Number of subjects analyzed. ** CFU/mL. † *P*-value was calculated by Fisher's exact test.
‡ Mean and standard deviation at baseline and final.
§ *P*-value was calculated by the Peto test and Peto's generalized Wilcoxon test.

Only two trials were included.[13,15] Both were conducted on pregnant mothers with baseline MS levels equal to or greater than 10^5 CFU/mL. In the first study, by Brambilla et al., 1,998, women in their third month of pregnancy visited the San Paolo Hospital, in Milan and were randomized into: (1) an experimental group, where mothers were given 0.05 percent sodium fluoride and 0.12 percent chlorhexidine mouthrinses to be used daily, starting from the end of the sixth month of pregnancy until delivery; and (2) a control group, whose members received only a minimal preventive program along with the study group. In the second included trial, by Nakai et al., conducted in a Japanese population in 2010, xylitol gums were given during pregnancy, and results were compared with those of a control group whose members received no gum. This review aimed to evaluate if there was a balance of important prognostic factors between the intervention and the control groups of both the included trials.

Both trials were assessed as having low risk of bias for this domain, since the differences between groups in prognostic factors such as MS levels in the mothers before intervention at baseline and minimal preventive measures in the study were not clinically important. However, in one trial,[15] systemic fluoride was also given to both groups as a baseline that might have affected the outcomes. Trials were excluded if complementary interventions, such as restorative procedures, were given to the participants along with the interventions. We anticipated that such intervention strategies would fail to answer our review question. In another study,[18] fluoride supplements in the form of tablets were given to the mothers during pregnancy, while fluoride supplementation as drops was given to the infants. This trial was not included, since the reviewers believed that it may have tended not to answer the exact review question.

Although we also sought information on the incidence of ECC, both the included trials primarily focused on the reduction of MS transmission. The outcome was measured by the evaluation of MS levels in children at six, 12, 18, and 24 months. However, in the study by Brambilla et al., MS levels of the children at nine months and the mothers' MS levels were also measured.

The study by Nakai[15] was assessed as having a high risk of bias, since the dropout rate was high. In fact, in this trial, 14 percent of the study population was evaluated as being at high risk of bias, with the remaining at unclear risk. Similar to clinical trials involving children over the long term, there was 17 percent attrition in the xylitol group and 39 percent attrition in the control group in this included trial; the reasons were clearly attributed to movement of families out of the study area and scheduling conflicts. It was also stated that no participants interrupted the study because of side effects of the xylitol chewing gum. Brambilla et al. did not provide any report on allocation concealment. The total number of dropouts was not reported. Only the number of participants excluded after randomization and the reasons for excluding them from the trial were stated. The absolute benefit from pharmacological interventions will, of course, depend on the expected caries increment in the form of ECC in the target population. We found scarce information regarding the effects of sodium fluoride and chlorhexidine mouthrinse on outcomes such as the number of children developing caries.

The overall quality of reporting of the two trials was poor. There was a substantial amount of heterogeneity in the body of evidence that addressed the main question of this review. Although the authors were unable to find a conclusive explanation for this, they noted a substantial variability between the trials included in this review concerning factors that may have potentially influenced the effect estimate in each study. Also, the geographic heterogeneity among both included studies could be a limitation, as the results can potentially be influenced due to variance in the distribution and prevalence of MS levels among different ethnic groups.[15] Even though the aforementioned interventions are generally considered safe and well accepted, clinicians and policymakers have been unable to assess the actual benefits of these interventions in preventing ECC. In the study by Brambilla et al., the authors justified a combined use of both sodium fluoride and chlorhexidine mouthrinse as producing a synergistic effect on the reduction of MS levels in mothers and children, with fluoride being the anticaries agent and chlorhexidine being the plaque-inhibitory agent. They also stated the advantages of this regimen as general acceptance by the participants, low cost, and the fact that it can be easily performed at home.

Gingivitis, an inflammation of tooth-supporting soft tissues without accompanying breakdown of the alveolar bone, occurs in 30 to 100 percent of pregnant women[45,46] and is associated with pathological changes in the oral microflora.[47] Prenatal interventions should not target only single bacteria but rather aim for the overall maintenance of the oral cavity during pregnancy, for the better oral health of the offspring. However, after the systematic review of both studies, no consensus was reached regarding the use of maternal pharmacological interventions on ECC incidence and MS transmission. Hence, their general clinical implementation is yet to be substantiated.

This report of only two trials may limit our ability to make recommendations. Nonetheless, the efficacy of prenatal pharmacological interventions targeting a single bacterium remains controversial, since other confounding risk factors may be overlooked. Thus, this review reveals a substantial need for higher-quality trials.

Conclusions

The results of this investigate support the following conclusion:

1. Statistically significant results were reported in both the included studies.
2. However, systematic analysis revealed a dearth of current evidence to support the general recommendation of pharmacological interventions for expectant mothers resulting in altered mutans streptococci levels in their children.

Acknowledgments

The authors wish to thank Prathap Tharyan, professor of Psychiatry and director, South Asian Cochrane Collaboration, Christian Medical College, Vellore, Tamil Nadu, India, for his valuable guidance throughout the review process, and Dr. William Glenn, DDS, President, Children Dental Research Society, Florida for her valuable comments.

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