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[Intervention Protocol]

Maternal consumption of xylitol for preventing dental decay in children

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To evaluate the effects of xylitol (consumed by mothers) at reducing tooth decay in their children compared with alternative treatments (e.g. chlorhexidine, fluoride varnish, placebo, or no treatment).
2. To assess 1 above (caries reduction in populations) at different levels of baseline caries risk.
3. To assess any reported changes in bacterial levels (of any species) in children/mothers.
4. To describe participant satisfaction levels.

BACKGROUND

Description of the condition

Dental caries is one of the most common preventable childhood diseases; people are susceptible to the disease throughout their lifetime (Selwitz 2007).

In many high-income countries caries prevalence has declined. However, disparities remain and many children and adults still develop caries (Selwitz 2007). In Aboriginal children in Western Australia, dental caries is the fifth and sixth most common disease causing hospitalisation in preschool children and primary school children respectively (Tennant 2000 as reviewed in Selwitz 2007). In the USA, caries is the most common chronic disease of childhood, and is five times more common than asthma (US Department of Health and Human Services). Dental caries is the primary cause of oral pain and tooth loss (US Department of Health and Human Services). It can be arrested and potentially reversed in its early stages, but is often not self limiting and without proper care, caries can progress until the tooth is destroyed (Fejerskov 2003).

Dental caries results from interactions over time between a biofilm containing bacteria that produces acid, a substrate (fermentable carbohydrates) that the bacteria can metabolise, and many other host factors including teeth and saliva (Selwitz 2007). According to Takahashi 2011, there are three stages in the caries process: a dynamic stability stage (with the dominance of *non-mutans*

Streptococci and actinomyces), an acidogenic stage (with low pH *non-mutans Streptococci* and actinomyces), and a severe/prolonged acidification stage (increase in *mutans Streptococci* and *non-mutans Streptococci* aciduric bacteria).

When these bacteria colonize the oral cavity, they form part of the biofilm (or plaque) that resides directly on the non-shedding tooth surface. The biofilm is complex containing at least several hundred species of bacteria (Selwitz 2007). No single bacterial species can predict caries development in a particular person (Selwitz 2007). However, evidence of high levels of *mutans Streptococci* is considered to be a strong risk factor for early childhood caries (Parisotto 2010).

The major reservoir from which infants acquire *mutans Streptococci* is the primary care giver, usually the mother (Berkowitz 2003; Seow 1998). Evidence suggests that *mutans Streptococci* can colonize the mouth of pre-dentate infants and are acquired by both vertical and horizontal transmission from human reservoirs (Berkowitz 2003).

Caries is related to lifestyle and behavioural factors within a person's control (e.g. poor oral hygiene, frequent consumption of refined carbohydrates (Fejerskov 2003)) but also factors not within their control including deprivation (Ramoz-Gomez 2002) and possibly genetic make-up (Werneck 2010). The international trend in caries management is towards prevention aiming to control the initiation and progression of the disease process over a person's lifetime (Selwitz 2007). Preventative dentistry aims to stop the progression of dental caries by oral hygiene regimens that either promote remineralization of teeth or prevent the formation of the biofilm responsible for lowering the oral pH levels (Takahashi 2011). Preventative methods which delay the colonization of *mutans Streptococci* can have a long-term influence on the caries experience of the child (Kohler 1994).

Description of the intervention

Xylitol

Xylitol is a naturally occurring 5 carbon polyol sweetener which is widely used in various sweets in Finland, some European countries, and Japan and Korea. Xylitol is one of a number of non-sugar sweeteners permitted for use in foods (Department of Health 1983). It is found naturally in some foods but it is mass-produced, principally from sustainable xylan-rich hardwood sources such as birch and beech wood.

Some research has suggested that xylitol has a unique, positive role in preventing dental caries (independent of its role in increasing saliva) (Makinen 1998; Milgrom 2009). Other studies refute xylitol's unique action suggesting that the caries-preventive effects of xylitol chewing gum can be explained adequately by the favourable action of chewing gum alone (Scheie 1998). It has also been observed in trials with xylitol-containing gums that the bacterial flora of plaque changes with the more cariogenic bacteria becoming less frequent (Maguire 2003).

Maguire suggests that xylitol may reduce the levels of *mutans Streptococci* in plaque through non-specific and specific effects (Maguire 2003).

1. Non-specific effects.
   - Xylitol does not act as a substrate for acid production in plaque; therefore does not encourage bacterial growth (Gehring 1973; Gehring 1976).
   - Xylitol reduces acidogenicity of plaque (Spleith 2009).
   - Xylitol reduces the amount and adhesivity of plaque (Soderling 1997).

2. Specific effects.
   - When *mutans Streptococci* are exposed to xylitol they can develop mutant xylitol-resistant strains which may be less virulent in the oral environment (Beckers 1988; Soderling 1997; Trahan 1992).
   - Exposure of plaque to xylitol leads to an increase in the concentrations of amino acids and ammonia, neutralising plaque acids (Makinen 1976; Makinen 1985; Soderling 1987).
   - Xylitol can act in a bacteriostatic way: some strains of oral streptococci take up xylitol and convert it to xylitol-5-phosphate, resulting in the formation of intra-cellular vacuoles and degraded cell membranes (Assev 1980; Pihlanto-Leppala 1990; Scheie 1998; Trahan 1985; Tuompo 1983).
   - Xylitol can cause a 'futile metabolic cycle'. Streptococcus strains take up xylitol and phosphorylate it to xylitol-5-phosphate. This is then split by sugar-phosphate phosphatases and the xylitol is then expelled from the cell (Pihlanto-Leppala 1990; Rogers 1991; Soderling 1989; Trahan 1991).

How the intervention might work

Having high levels of *mutans Streptococci* is a risk factor for early childhood caries (Parisotto 2010). Xylitol shows specific *mutans Streptococci*-inhibiting effects (Maguire 2003; Trahan 1995). Xylitol consumption does decrease counts of *mutans Streptococci*, although the mechanism behind this decrease is not well understood (Maguire 2003; Soderling 2010). A number of researchers have reported that habitual maternal consumption of xylitol reduced the probability of mother-child transmission of *mutans Streptococci* (Nakai 2010; Soderling 2000), although Thorild 2003 and Fontana 2009 found no statistically significant effect. Theoretically a reduced transmission of cariogenic bacteria such as *mutans Streptococci* from mother to child could lead to subsequent reduction in children's dental decay, and this has been demonstrated by Isokangas 2000 and Olak 2012.

Why it is important to do this review

There are a small number of mother-child studies involving the maternal consumption of xylitol and its effect on childhood dental caries (Fontana 2009; Isokangas 2000; Nakai 2010; Olak 2012; Thorild 2006). However, there is also controversy over the benefits of xylitol when used in this manner. A systematic review is needed to identify and evaluate any other relevant research in this area using Cochrane criteria.

OBJECTIVES

1. To evaluate the effects of xylitol (consumed by mothers) at reducing tooth decay in their children compared with alternative treatments (e.g. chlorhexidine, fluoride varnish, placebo, or no treatment).

2. To assess 1 above (caries reduction in populations) at different levels of baseline caries risk.

3. To assess any reported changes in bacterial levels (of any species) in children/mothers.

4. To describe participant satisfaction levels.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Types of participants

Pregnant and post-partum mothers (female) who at the time of commencing the research project had a child not older than 12 months.

Types of interventions

Daily consumption of any reported dosage of xylitol with no prolonged break (greater than 1 month), in any oral format (e.g. chewing gum, mints, lozenges, mouthrinses, toothpaste) compared with placebo, no treatment, caries preventive treatments (e.g. anti-plaque or anti-calculus agents, oral hygiene interventions or topical fluorides).

Acceptable placebo groups will be using any sham products sweetened with sugars (sucrose, fructose, glucose, etc), sugar products (honey, high fructose corn syrup, etc), non-nutritive sweeteners (saccharin, aspartame, cyclamates, etc), or sugar alcohols other than xylitol (sorbitol, mannitol, etc).

Types of outcome measures

Primary outcomes

Caries reduction as measured by:

- child's dental caries at both the enamel and dentinal level of diagnosis, measured using any index (e.g. DMFT, dmft, ICDAS, etc)
- child caries experience: yes/no
- prevented fraction (PF).

Secondary outcomes

- Mother's dental caries using any index (e.g. DMFT, dmft, ICDAS, etc).
- Mother's plaque.
- Child's plaque.
- Child's bacterial levels of any species.
- Mother's bacterial levels of any species.
- Adverse effects (of any kind) associated with xylitol consumption.
- Participant satisfaction level.

Search methods for identification of studies

For the identification of studies included or considered for this review, detailed search strategies will be developed for each database searched. These will be based on the search strategy developed for MEDLINE via OVID (Appendix 1) but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The strategy will consist of controlled vocabulary and free text terms.

The search strategy will combine the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying reports of randomised controlled trials in MEDLINE via OVID (as published in box 6.4.c in the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (updated March 2011) (Higgins 2011).

The search will attempt to identify all relevant studies irrespective of language. Non-English papers will be translated with assistance from NHS Fife, and the Cochrane Oral Health Group.

Electronic searches

The following databases will be searched:

- The Cochrane Oral Health Group's Trials Register (whole database)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue)
- MEDLINE via OVID (1950 to present)
- EMBASE via OVID (1980 to present)
- CINAHL via EBSCO (1982 to present)

- LILACS via BIREME (1982 to present)
- Dissertations and theses via ProQuest (1950 to present)
- ZETOC conference proceedings (1993 to present)
- Web of Science conference proceedings (1990 to present)
- ClinicalTrials.gov (whole database)
- *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) (whole database).

Searching other resources

The *Journal of Dental Research* has been identified as a journal which should be handsearched for this review. This journal has already been searched as part of the Cochrane Journal Handsearching Programme from 2003, the journal will be handsearched by the review authors from 2000 to 2002.
The reference lists of all eligible trials will be checked for additional studies.

Data collection and analysis

The titles and abstracts (when available) of all reports identified through the searches will be scanned independently by two review authors (Brett Duane (BD) and Derek Richards (DR)).

Selection of studies

Full reports will be obtained for trials appearing to meet the inclusion criteria or for which there is insufficient information in the title and abstract to make a clear decision. The full reports obtained from all the electronic and other methods of searching will be assessed independently, in duplicate, by two review authors to establish whether the trials meet the inclusion criteria or not. Disagreements will be resolved by discussion. Where resolution is not possible, an independent author will be consulted. All studies rejected at this or subsequent stages will be recorded in the table of excluded studies and reasons for exclusion will be recorded.

Data extraction and management

Data will be extracted by two review authors (BD and DR) independently using properly developed data extraction forms. The data extraction forms will be piloted on several papers and modified as needed before use. Any disagreement will be resolved by discussion and an independent author will be consulted where necessary. If agreement cannot be reached data will be excluded until further clarification is provided. For each trial the following data will be recorded.

1. Author, journal, date of the study, year of publication, country of origin and source of study funding.
2. Details of the participants including demographic characteristics (of both mother and child) and criteria for inclusion.
3. Randomisation type (i.e. cluster randomised trial, individual).
4. Details of the age of the child when the xylitol was commenced.
5. Details on the type of intervention (i.e. the form of xylitol (e.g. gum/lozenge, etc)).
6. Details of the dosage of product consumed (frequency/dosage per session/daily dosage).
7. Details of the comparison products (e.g. xylitol product compared with sorbitol sweet, mannitol sweet, fluoride varnish, etc).
8. Details of the length of time the xylitol was consumed.
9. Details of the outcomes reported (tooth decay, adverse effects, participant satisfaction level, dose response, bacterial levels measured, mother dental health), including method of assessment and time intervals after intervention.
10. Reliability of primary outcome measure: number of examiners; calibration; method of clinical assessment.
11. Side effects.

Assessment of risk of bias in included studies

All trials included in the review will be assessed for risk of bias independently and in duplicate as part of the data extraction process.
The trials will be assessed for risk of bias using the domain-based evaluation tool, specifically developed by The Cochrane Collaboration. This tool, described in the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (updated March 2011) (Higgins 2011) is a two-part tool, addressing seven specific domains namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Each domain includes one or more specific entries in a risk of bias table. Within each entry, the first part of the tool will describe what was reported to have happened in the study, in sufficient detail to support a judgement about the risk of bias. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by assigning a judgement of low risk of bias, high risk of bias or unclear risk of bias (Higgins 2011).
A risk of bias table will be completed for each included study and results for all studies collated graphically. This will identify both individual studies and particular domains with high risk of bias, both of which can be explored further in sensitivity analyses.

Measures of treatment effect

For caries experience (a binary outcome variable), risk ratios (RR) and 95% confidence intervals will be presented. For continuous outcome data, means, standard deviations and sample sizes will be presented in order that standardized mean differences can be analysed. The prevented fraction (PF), defined as the mean difference

in the control group minus the mean difference in the treatment group, divided by the mean difference in the control group, will be considered if different studies have presented caries reduction in different ways. Variances and confidence intervals for the PF will be calculated within Stata using the user derived program: fielleri.ado (version 1.0 2004-12-07, Joseph Coveney) (Abrams 1980).

The contrast between the outcomes of all groups (the 'treatment effect') will be provided by considering four questions:

1. What is the direction of effect?
2. What is the size of effect?
3. Is the effect consistent across studies?
4. What is the strength of evidence for the effect?

Meta-analysis where possible will provide a statistical method for questions 1 to 3. Assessment of question 4 will rely on an assessment of study design and risk of bias, as well as statistical measures of uncertainty.

Unit of analysis issues

In each study the following unit of analysis issues will be considered.

1. Groups of individuals were randomised together to the same intervention (i.e. cluster randomised trials).
2. Multiple observations for the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).
3. Multiple intervention groups (studies that compare more than two intervention groups will be included in meta-analysis by making multiple pair-wise comparisons between all possible pairs of intervention groups).

Dealing with missing data

Where data are missing trial authors will be contacted. Data will be excluded until further clarification is available or if agreement cannot be reached. In cases where standard deviations (SDs) for caries difference are missing, the method recommended by Van Rijkom 1998 whereby linear regression of log transformed standard deviations on log transformed mean caries reductions is used to impute the SDs where appropriate.

Assessment of heterogeneity

Heterogeneity will be assessed in two ways.

1. Primarily, visual inspection of the forest plots, in particular of the estimates and 95% confidence intervals of the treatment effects.
2. The I^2 statistic from meta-analysis will give a reasonable indication of whether account has to be taken in the modelling process of heterogeneity.

Assessment of reporting biases

Multiple sources of publications will be sourced, including data from unpublished trials (where available on online trial registries as outlined in the search criteria).

Data synthesis

Meta-analysis, if appropriate, will use random-effects models for incorporating unexplained heterogeneity.

Subgroup analysis and investigation of heterogeneity

Where possible, subgroup analysis will be conducted to assess:

1. differences in effect between types of xylitol products (chewing gum, mints, lozenges, mouthrinses, toothpaste, other);
2. differences in effect between high and low dose and frequency of product;
3. differences in effect between different levels of baseline and caries risk.

Variation across studies (heterogeneity) will be considered, if sufficient studies exist to allow the reliable investigation of the reasons for it.

Clinical heterogeneity will be assessed by examining the types of participants, interventions and outcomes in each study.

Sensitivity analysis

A sensitivity analysis will be performed both with and without outlying studies.

A sensitivity analysis will take place repeating the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear.

Sensitivity analysis will be undertaken to assess the effects of:

1. excluding studies with high risk of bias, in particular in domains: random sequence generation, allocation concealment and blinding;
2. excluding unpublished studies (if there are any); and
3. excluding studies funded by companies that produce confectionery or xylitol products (e.g. Xlear, etc).

Presentation of main results

A 'Summary of findings' table will be developed for the primary outcomes of this review using GRADEPro software. The quality of the body of evidence will be assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, the risk of publication bias, the magnitude of the effect and whether or not there is evidence of a dose response. The quality of the body of evidence for each of the primary outcomes will be categorised as high, moderate, low or very low.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

1. exp DENTAL CARIES/
2. (teeth adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
3. (tooth adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
4. (dental adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
5. (enamel adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
6. (dentin adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
7. (root adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
8. Dental plaque/
9. ((tooth or teeth or dental or saliva$) adj4 (plaque or "mutans strep$" or strep$ mutans)).mp.
10. exp TOOTH DEMINERALIZATION/
11. or/1-10
12. exp Sugar Alcohols/
13. ("sugar alcohol$" or polyol$).mp.
14. exp Sweetening Agents/
15. sweetener$.mp.
16. xylitol/
17. xylitol.mp.
18. or/12-17
19. infectious disease transmission, vertical/
20. ((maternal adj4 transmission) or (mother$ adj4 transmission) or (parent$ adj4 transmission)).mp.
21. ((maternal adj4 acquisition) or (mother$ adj4 acquisition) or (parent$ adj4 acquisition)).mp.
22. ((maternal adj4 transfer$) or (mother$ adj4 transfer$) or (parent$ adj4 transfer$)).mp.
23. ("mother to child" or mother-to-child or "parent to child" or parent-to-child).mp.
24. ("mother to infant" or mother-to-infant or "parent to infant" or parent-to-infant).mp.
25. Mother/
26. Child/
27. Infant/
28. 25 and (26 or 27)
29. ((mother$ or maternal or parent$) and (child$ or infant$ or baby or babies or toddler)).mp.
30. Pregnancy/
31. (pregnan$ or foetus or fetus or foetal or fetal or "in utero").mp.
32. 19 or 20 or 21 or 22 or 23 or 24 or 28 or 29 or 30 or 31
33. 11 and 18 and 32

HISTORY

Protocol first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Derek Richards (DR) and Brett Duane (BD) co-ordinated the review, and collected data. Anne Littlewood (AL) and BD developed the search strategy; BD will undertake the searching; BD and DR plan to screen the titles and abstracts; BD will organise retrieval of papers; BD and DR will screen retrieved papers against the inclusion criteria, appraise the quality of the papers, and extract data; BD will obtain and screen data on unpublished studies and additional data on published studies; BD will enter data into RevMan, be responsible for data management for the review. DR, BD and Andrea Sherriff (AS) will analyse the data; BD, DR and AS will interpret the data; DR and BD will write the review.

DECLARATIONS OF INTEREST

Brett Duane (Chief investigator) and Derek Richards (Principal investigator) are leading a randomised controlled trial investigating the maternal consumption of xylitol to reduce early childhood caries in children. Full details of the protocol are registered on http://clinicaltrials.gov/ct2/show/NCT01038479.

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