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Effect of Mode of Delivery on Early Oral Colonization and Childhood Dental Caries: A Systematic Review

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Keywords
Childhood · Colonization · Dental caries · Cesarean section

Abstract
This review investigated whether mode of delivery influences the colonization of infant's oral cavity and the risk of early childhood caries (ECC). The search strategy included systematic searching of electronic databases (Web of Science and PubMed) for articles published (1995–2015) and hand searching of references lists. Outcomes of interest were the presence of oral caries-related microorganisms, oral species considered protective against caries, and dental caries. Other outcomes included severity of dental caries, dental claims, and age at first dental visit. Study quality was assessed using the EPHPP tool. For each study, we present odds ratios and respective 95% confidence intervals for the association between these outcomes and the mode of delivery. Fourteen studies were identified. In 5 out of 8 studies addressing oral colonization, children born by cesarean section were less likely to harbor caries-related microorganisms as well as protective bacteria against caries and acquired caries-related microorganisms earlier, when compared with vaginally delivered children. No consistent results were obtained for the association between mode of delivery and dental caries. Although there were differences in oral colonization by mode of delivery, it seems that other determinants rather than mode of delivery could be major contributors to the development of ECC.

Efeito do tipo de parto na colonização oral e cárie dentária nas crianças: Revisão sistemática da literatura

Palavras chave
Infância · Colonização oral · Cáries dentárias · Cesariana

Resumo
Esta revisão investigou se o tipo de parto influencia a colonização da cavidade oral do bebé e o risco de cárie precoce na infância (CPI). A estratégia de pesquisa incluiu a pesquisa sistemática em bases de dados eletrónicas (Web of Science e PubMed) para artigos publicados (1995–2015) e a pesquisa manual de listas de referências.

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Os principais resultados apontaram para a presença de microrganismos relacionados com a cárie oral, espécies orais consideradas protetoras contra a cárie e a cárie dentária. Outros resultados obtidos incluíram a gravidade da cárie dentária, as reclamações odontológicas e a idade na primeira consulta odontológica. A qualidade do estudo foi avaliada usando a ferramenta EPHPP. Para cada estudo apresentamos odds-ratio (OR) e respetivos intervalos de confiança de 95% (IC 95%) para a associação entre esses desfechos e o tipo de parto. Foram identificados catorze estudos. Em cinco de oito estudos abordando a colonização oral, as crianças nascidas por cesariana foram menos propensas a abrigar microrganismos relacionados com a cárie, bem como bactérias protetoras contra a cárie e micro-organismos relacionados com cárie adquirida anteriormente, quando comparadas com crianças nascidas de parto vaginal. Não foram obtidos resultados consistentes para a associação entre o tipo de parto e a cárie dentária. Embora houvesse diferenças na colonização oral por tipo de parto, parece que outros determinantes, em vez do tipo de parto, podem ser os principais fatores que contribuem para o desenvolvimento da CPI.

Introduction

Early childhood caries (ECC) has been defined as the presence of decayed tooth surfaces among children up to 6 years old and is the most common chronic childhood disease [1]. ECC is related to oral pain which has adverse effects on children such as lost sleep, eating problems, behavioral problems, and reduction in preschool or school attendance [1, 2]. Moreover, advanced forms of ECC usually require general anesthesia for treatment [2]. Therefore, ECC emerges as an important public health issue with significant economic impact [3], and it deserves particular attention with regard to the factors that define the risk profile of children.

The presence of cariogenic microorganisms on tooth surfaces plays an essential role in the occurrence of dental caries [4–6]. *Streptococcus mutans* and *Streptococcus sobrinus* (often considered a group called mutans streptococci), have been considered the most common acid producers associated with the carious lesion [4, 6–9]. These bacterial species along with *Streptococcus salivarius* were associated with caries [8], particularly among young children [6, 8, 9].

Successful colonization by mutans streptococci depends on the number of other commensal bacteria already present in the oral cavity because they need to compete for nutrients [7, 10]. Therefore, as the density of other pioneer oral microbiota increases, the chance of successful colonization by mutans streptococci will decrease. Furthermore, a number of common plaque microorganisms such as *Streptococcus sanguinis* and *Streptococcus gordonii* are able to catabolize the amino acid arginine to ammonia favoring a pH rise [8, 10, 11] which could counteract the harmful effect of low pH on the tooth surface. Therefore, bacterial colonization in a child's mouth is the most important event underlying the pathogenesis of ECC.

Oral colonization starts at birth by vertical transmission from mother to child [12]. The birth canal presents a high density of microorganisms which might be acquired by vaginally delivered babies [13]. By comparison, the exposure to maternal microorganisms is dramatically weakened among newborns delivered by cesarean section resulting in atypical oral microbiota. Accordingly, it has been postulated that babies born by cesarean section are vulnerable to early oral colonization by cariogenic microorganisms and they will present increased risk of ECC [14].

There has been a dramatic rise in rates of cesarean section over recent decades [15]. In a public health perspective, it seems important to know whether infants delivered by cesarean section should be considered a risk group for ECC in order to intensify preventive measures against dental caries among these children.

Therefore, the aim of this study was to present a systematic review of evidence on whether mode of delivery has an impact on colonization of infant's oral cavity and on the risk of childhood dental caries.

Methods

Search Strategy

Our systematic review was performed according to the procedures of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. However, the protocol of the study was not registered. A comprehensive electronic search of relevant literature was conducted in Web of Science (Thomson Reuters) and PubMed databases for articles published over the last two decades (January 1995 – March 2016). We used keywords for each of the following items: (1) population ("infant," "child*," "newborn"); (2) exposure ("mode of delivery," "delivery mode," "surgical delivery," "cesarean delivery," "caesarean delivery," "cesarean section," "caesarean section," "c-section," "birth," "childbirth"); and (3) outcome ("streptococ*," "lactobacil*," "bacteria*," "oral health," "dental health," "caries" OR "dental caries," "dental de-

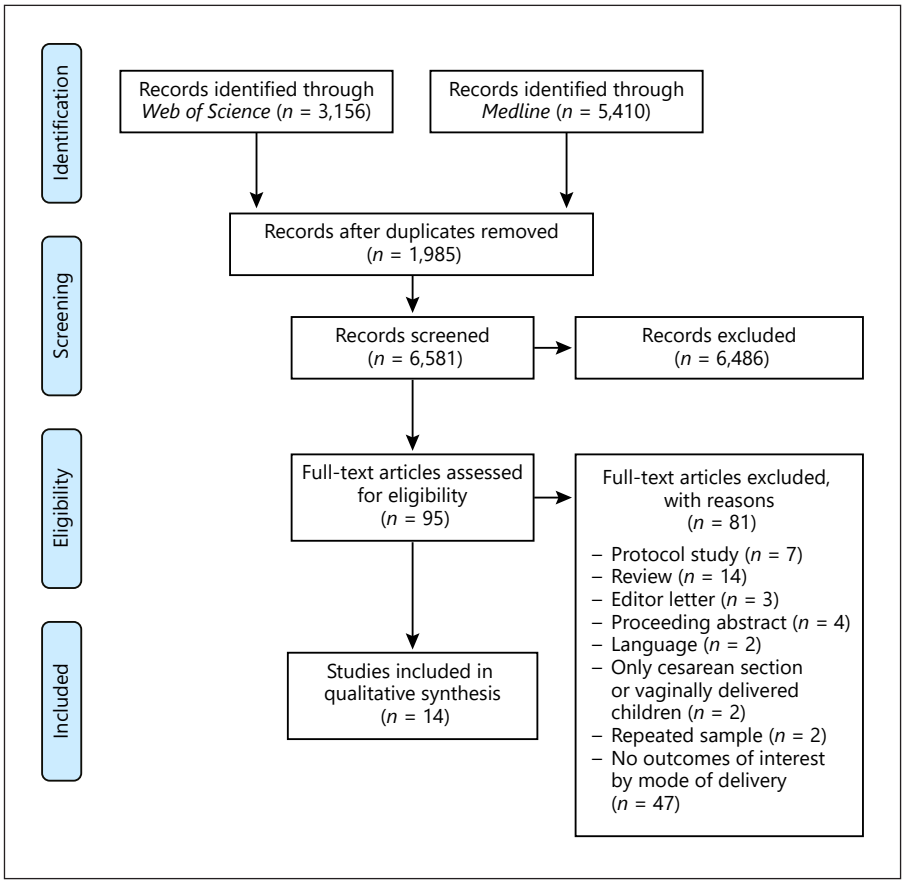

Fig. 1. Flowchart (PRISMA statement) presenting study selection.

cay," "tooth decay," "teeth decay," "decayed tooth," "decayed teeth," "decayed-missing-filled-teeth," "dmft," "early childhood caries," "oral bacteria," "oral bacterial community," "oral biota," "oral pioneer community," "oral micro*," "oral acquisition," "oral colonization").

Eligibility Criteria

We included all types of observational (cohort, cross-sectional, and case-control) studies reporting results about the effect of mode of delivery on early oral colonization and ECC among children 6 years old or younger. The exposure of interest was the mode of delivery defined as cesarean section versus vaginal delivery. Our outcomes of interest were: (1) prevalence of caries-associated species: *S. mutans*, *S sobrinus*, and *S. salivarius*; (2) prevalence of microbial protective factors against caries: *S. sanguinis* and *S. gordonii*; (3) prevalence of dental caries; (4) severity of dental caries assessed by the mean of decayed-missing-filled tooth (DMFT) and decayed-missing-filled tooth surface (DMFS) index; (6) other outcomes included dental claims and time of first dental caries.

Studies were eligible if they presented the results using measures of association (odds ratio [OR], relative risk, or hazard ratio) between the mode of delivery and the outcomes of interest, or raw data were available in order to compute them, or information about differences between groups by mode of delivery for outcomes of interest were provided throughout the paper.

We excluded case report studies, literature reviews, letters to the editor, study protocols, and studies in languages other than English, Portuguese, French, and Spanish.

Study Selection

The titles and abstracts of all references obtained were scrutinized and the full text of potentially eligible citations was retrieved for further assessment. Two authors (C.A. and C.T.) screened titles and abstracts to exclude citations beyond the scope of this review. Abstracts reporting the association between perinatal factors (birthweight, gestational age, pregnancy or delivery factors, and breastfeeding) and outcomes of interest were considered potentially eligible citations. A further selection was conducted by all the authors who independently reviewed the full text of the abstracts identified as potentially eligible citations. Disagreements were settled by consensus discussion.

Additionally, the reference lists of selected citations were screened to identify further relevant studies using the same inclusion criteria.

Methodological Quality Assessment

For quality assessment, we used the Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (QAT-EPHPP) [17, 18]. This tool assesses the strength of the studies across six methodological items (selection bias, study design, confounders, blinding, data collection methods,

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Table 1. Characteristics of studies included in the systematic review

First author [Ref.], year (country)	Type of study	Sample size	Children's age	Outcome assessed					Methods	Positive outcome	QAT-EPHPP rating
				presence of bacteria	ECC pre-valence	DMFT DMFS	claims for oral health	time until 1st caries			
Boustedt [25], 2015 (Sweden)	Prospective cohort	V = 95 CS = 53	1, 3 and 6 months old	✓					Saliva sampling	More than 10^4 cells per mL	Moderate
Yepes [20], 2014 (USA)	Retrospective cohort	V = 5,051 CS = 291	Less than 5 years old				✓		Claims filed through Medicaid	Codes for the type of visit	Strong
Sayyed [26], 2014 (Saudi Arabia)	Retrospective cohort	170	3–5 years old		✓				Dental examination	Probe sticks in tooth defect	Moderate
Reed [27], 2014 (Finland)	Prospective cohort	V = 83 CS = 20	4–6 weeks old	✓					Saliva sampling	More than 10^4 cells per mL	Moderate
Nelson [21], 2014 (USA)	Prospective cohort	V = 189 CS = 184	At 8 and 18–20 months old	✓					Saliva sampling	More than 10^4 cells per mL	Strong
Kuthy [22], 2014 (USA)	Retrospective cohort	V = 134 CS = 53	Less than 6 years old					✓	Review of dental charts	Type of dental visit	Strong
Zhou [23], 2013 (China)	Prospective cohort	225	8–32 months old	✓					Plaque samples	More than 10^4 cells per mL	Strong
Pattanaporn [24], 2013 (Thailand)	Cross-sectional	V = 184 CS = 166	3–5 years old		✓	✓			Dental examination	Detectable white-spot lesion or cavity	Weak
Thakur [28], 2012 (India)	Prospective cohort	V = 30 CS = 30	Less than 1 year old	✓					Saliva or plaque sampling	Presence for two consecutive samples	Moderate
Barfod [19], 2012 (Denmark)	Retrospective cohort	V = 443 CS = 151	At 3 years old		✓	✓			Governmental databases	Information on DMFS	Strong
Zhou [29], 2011 (China)	Cross-sectional	V = 231 CS = 163	At 2 years old		✓					One or more DMFT	Moderate
Lif Holgerson [30], 2011 (Sweden)	Cross-sectional	V = 25 CS = 38	At 3 months old	✓					Swabbing oral mucosa	More than 10^4 cells per mL	Moderate
Barfod [31], 2011 (Sweden)	Cross-sectional	V = 42 CS = 41	6–10 months old	✓					Saliva sampling	More than 10^4 cells per mL	Moderate
Li [14], 2005 (USA)	Prospective cohort	V = 127 CS = 29	Less than 4 years old	✓					Saliva and plaque sampling	Colony morphology	Moderate

DMFT, decayed missing filled tooth; DMFS, decayed missing filled tooth surface; V, vaginal delivery; CS cesarean section, QAT-EPHPP, Quality Assessment Tool - Effective Public Health Practice Project.

Table 2. Association between the mode of delivery and the prevalence of salivary cariogenic-related species stratified by children's age (reference group: vaginal delivery)

Child age	Boustedt [25], 2015 (n = 148)	Nelson [21], 2014 (n = 373)	Zhou [23], 2013 (n = 225)	Thakur [28], 2012 (n = 60)	Reed [27], 2014 (n = 103)	Holgerson [30], 2011 (n = 63)	Barfod [31], 2011 (n = 83)	Li [14], 2005 (n = 156)	Pattanaporn [24], 2013 (n = 350)
***S. mutans* (or mutans streptococci)**									
2 days	0.36 (0.18–0.83)								
1 month	0.23 (0.09–0.59)				0.35 (0.04–2.84)				
3 months	0.20 (0.08–0.50)					Lower for CS group[a]			
6 months	2.14 (0.59–7.84)			1.56 (0.24–10.1)					
9 months				2.00 (0.62–6.47)					
6–10 months							0.44 (0.18–1.08)		
12 months				1.53 (0.54–4.36)					
18 months		0.69 (0.45–1.043)							
8–32 months			1.17 (0.82–1.68)[b]						
48 months								0.79 (0.33–1.88)	
36–60 months									0.55 (0.35–0.91)
S. salivarius									
2 days	0.71 (0.34–1.47)								
1 month	0.39 (0.19–0.83)								
3 months	0.43 (0.20–0.95)								
6 months	0.39 (0.18–0.86)								
6–10 months							0.21 (0.08–0.58)		
Confounding management	A	B	C	D	E	F	G	H	I

Values indicate OR (95% CI). CS, cesarean section. Unadjusted estimates computed from raw data (A, B, D, E, G, and H) or provided by the authors (C). Adjusted for gestational age, infant age, tooth brushing, prechewing food by caregivers and mother's mutans streptococci level and alcohol drinking (I). Comparison between groups by mode of delivery was not provided (B and C), was provided for one potential confounder (D and E), or for several potential confounders (A, G, and H). Accordingly, groups were similar for gender, siblings, infant feeding, pacifier use and maternal education, country of origin, smoking and antibiotics (A), for gender length and weight at birth and at 3 months old, breastfeeding (F), for gender, gestational age, siblings, finger sucking, antibiotics, probiotics, tooth brushing, fluoride toothpaste, mother's education and country of origin (G), for birthweight, gestational age, family income and maternal age, weight gain, cigarette smoking, alcohol drinking, *S. mutans* level in saliva and sexually transmitted infections (H), for gender (B), and for breastfeeding (C). [a] Measures of association or raw data were not provided. Information retrieved from a graphic. [b] Based on total sample of five examinations rather than number of children.

and withdrawals/dropouts). Studies are rated weak, moderate, or strong on each methodological item, and a global rate for each study is obtained as follows: strong (if no weak ratings), moderate (if one weak rating), and weak (if the study presents 2 or more weak ratings) [18]. We intended to include all studies reporting results about the effect of the mode of delivery on the outcomes of interest, independent of the main objective presented by the authors. Therefore, for some studies the mode of delivery could appear as one of several determinants or as a potential confounder rather than the exposure of interest. Taking into account such circumstance, we did not consider the item of QAT-EPHPP asking about confounders. However, we retrieved information on adjusted measures of association or whether groups by mode of delivery have similar distribution of potential confounding factors.

Two reviewers (C.A. and C.T.) independently assessed the methodological quality of studies. Any discrepancies between reviewers concerning the item ratings were resolved through discussion and, when necessary, a third reviewer (M.J.G.) was consulted.

Data Extraction

Authors independently extracted information from each eligible study based on the following data: first author, publication year, sample size, type of study, age of participants, outcome of interest, criteria to define outcome of interest, and estimates of measures of association between mode of delivery and outcomes of interest.

Data Synthesis

Due to large differences of the included studies with regard to the study design, methods for sample recruitment and particularly age of children evaluated, meta-analysis was not performed. For each study, the OR and respective 95% confidence interval (95% CI) for the association between mode of delivery and the outcome of interest were obtained. Vaginally delivered children were considered the reference group. When necessary, the equivalent of OR and respective 95% CI were computed. When measures of association were not provided by the authors, OR and 95% CI were computed from raw data retrieved from tables or from the text. Thus, the number of positive and negative outcomes for each group by mode of delivery was extracted from studies, and the OR and respective 95% CI were computed. Moreover, mean and respective standard deviation for DMFT, DMFS and the age at *S. mutans* acquisition were retrieved from studies. All results were stratified according to the age of children as provided by the authors.

Results

As described in detail in the flowchart (Fig. 1), the search strategy yielded 14 studies meeting the established criteria. The main characteristics of the studies including the outcomes assessed are described in Table 1. According to the methodological quality assessment, 5 studies were classified as strong [19–23], 1 study as weak [24], and the remaining studies were considered moderate [14, 25–31].

Table 3. Association between the mode of delivery and the prevalence of salivary *S. sanguinis* and *S. gordonii* by children's age (reference group: vaginal delivery)

Child age	Boustedt [25], 2015 (n = 148)	Lif Holgerson [30], 2011 (n = 63)	Barfod [31], 2011 (n = 83)
S. sanguinis			
2 days	0.02 (0.001–0.29)		
1 month	0.06 (0.01–0.26)		
3 months	0.11 (0.04–0.34)	Lower for CS group[a]	
6 months	0.14 (0.05–0.37)		
6–10 months			0.45 (0.18–1.14)
S. gordonii			
2 days	0.35 (0.10–1.27)		
1 month	0.53 (0.18–1.58)		
3 months	0.33 (0.12–0.89)	Lower for CS group[a]	
6 months	0.25 (0.10–0.67)		
6–10 months			1.46 (0.57–3.75)
Confounding management	A	B	C

Values indicate OR (95% CI). CS, cesarean section. Unadjusted estimates computed from raw data (A and B). Comparison between groups by mode of delivery was provided for several potential confounders (A, B, and C). Accordingly, groups were similar for gender, siblings, infant feeding, pacifier use and maternal education, country of origin, smoking and antibiotics (A), for gender length and weight at birth and at 3 months old, breastfeeding (B), and for birthweight, gestational age, family income and maternal age, weight gain, cigarette smoking, alcohol drinking and sexually transmitted infections (C). [a] Measures of association or raw data were not provided. Information retrieved from a graphic.

Prevalence of Children Who Present Cariogenic-Related Species

Eight studies [14, 21, 23, 25, 27, 28, 30, 31] showed results on differences between groups by the mode of delivery in the prevalence of children with *S. mutans* (or mutans streptococci) and/or *S. salivarius*. Results were stratified according to the children's age and summarized in Table 2. The prevalence of children with positive status varied across studies, ranging from 4.8 [30] to 79.9% [25] for *S. mutans* and from 53.3 [25] to 67.5% [31] for *S. salivarius*.

With regard to the colonization by *S. mutans,* there were no consistent results across studies. Three studies rated weak [24] to moderate [25, 30] in quality assessment reported significant lower frequency of *S. mutans* detection among infants born by cesarean section compared with those vaginally delivered but only among younger groups (2 days, 1 month, and 3 months old). Instead, 6 studies that were considered to have moderate [14, 27, 28, 31] to strong [21, 23] methodological quality reported no significant differences in prevalence of oral colonization by *S. mutans* between groups by mode of delivery (Table 2).

Two studies [25, 31] rated as moderate in quality assessment provided data on prevalence of salivary *S. salivarius* by mode of delivery. In both studies, cesarean section appeared as a protective factor against presence of *S. salivarius* in saliva for children aged between 1 and 10 months (Table 2).

Prevalence of Children Who Present Protective Species against Caries

Three studies that scored moderate [25, 30, 31] in methodological quality assessed the association between mode of delivery and the prevalence of both salivary *S. sanguinis* and *S. gordonii*. The prevalence of salivary microorganisms varied across studies ranging from 6.4 [30] to 65% [31] for *S. sanguinis* and from 4.8 [30] to 30.0% [31] for *S. gordonii*.

In 2 studies [25, 30], salivary *S. sanguinis* and *S. gordonii* were detected less frequently from cesarean section compared with vaginally born infants, although differences in *S. gordonii* detection lose their statistical significance among infants aged 2 days and 1 month. However, the third study [31] reported no significant differences in oral colonization pattern of *S. sanguinis* and *S. gordonii* by mode of delivery (Table 3).

Table 4. Prevalence of ECC by mode of delivery (reference group: vaginal delivery)

Child age	Studies	*n*	Caries prevalence, %	OR (95% CI)	Confounding management
2 years	Zhou [29], 2011	394	27.7	0.69 (0.43–1.08)	A
3 years	Barfod [19], 2012	594	8.1	0.77 (0.30–1.80)	B
3–5 years	Sayyed [26], 2014	170	Not available	1.17 (0.76–1.76)	C
	Pattanaporn [24], 2013	350	67.0	0.55 (0.35–0.86)	D

Unadjusted estimates computed from raw data and comparison between groups by mode of delivery was not provided (A). Adjusted estimates for educational level and family income (B), for maternal age, education level, gravidity, family income, gestational age, pre-eclampsia, Apgar scores, birth weight, age and gender of children, infant feeding and dietary habits during childhood (C), and for infant age, tooth brushing, prechewing food by caregivers and mother's mutans streptococci level and snack consumption (D).

Table 5. Severity of dental caries by mode of delivery

Study	Age, years	DMFT			DMFS		
		vaginal delivery	cesarean section	*p* value	vaginal delivery	cesarean section	*p* value
Barfod [19], 2012	3				0.2±1.4	0.4±3.0	>0.05
Pattanaporn [24], 2013	3	3.2±3.8	2.3±3.7	0.023	6.8±10.3	4.3±7.6	0.022
	5	5.6±4.9	5.1±5.1	>0.05	12.1±15.7	12.2±16.5	>0.05

Values are presented as mean ± standard deviation. DMFT, decayed missing filled tooth; DMFS, decayed missing filled tooth surface.

Prevalence of Dental Caries

Four studies presented results on caries prevalence by mode of delivery [19, 24, 26, 29]. The prevalence of caries varied across studies, ranging from 8.1 [19] to 67.0% [24]. A study that scored weak [24] reported significant differences in prevalence of dental caries by mode of delivery among children aged 3–5 years such that children born by cesarean section presented lower odds of dental caries than those vaginally delivered. Three studies that scored moderate [26, 29] to strong [19] reported no differences in dental caries prevalence between groups by mode of delivery (Table 4).

Severity of Dental Caries

Two studies compared groups by mode of delivery with regard to DMFT and DMFS; one reported results about children aged 3 years [19], and the other presented stratified results at age 3 and 5 years [24].

Among children aged 3 years, there were no consistent results between studies. A study rated strong reported a DMFS mean twice as high among children born by cesarean section in comparison with vaginally delivered children (0.4 ± 3.0 vs. 0.2 ± 1.4) [19], although with no statistical significance. Instead, a study [24] rated as weak reported statistically significant lower DMFS mean (4.3 ± 7.6 vs. 6.8 ± 10.3) and lower DMFT mean (2.3 ± 3.7 vs. 3.2 ± 3.8) among children born by cesarean section when compared with their vaginally delivered counterparts. The same study also [24] reported data on dental caries prevalence among children aged 5 years, and no differences were found between groups by mode of delivery, neither for DMFS nor for DMFT (Table 5).

Other Outcomes

A study rated as strong in quality assessment [20] provided data on dental claims among children of 5 years old that indirectly reflects ECC. After adjusting for birth weight, age at first dental visit and mother's ethnicity, no significant differences were found by mode of delivery neither for restorative (OR = 1.25; 95% CI: 0.86–1.66) nor

emergency (OR = 1.25; 95% CI: 0.90–1.66) claims. A moderate quality study reported that mode of delivery was significantly associated with earlier *S. mutans* acquisition [14], so that children born by cesarean section acquired *S. mutans* at a younger age than vaginally delivered children (mean age in months: 17.1 ± 1.8 vs. 28.8 ± 1.8; $p = 0.038$). This association remained significant even after adjustment for maternal factors (age, education level, income, regular cigarette smoking and alcohol drinking, use of antibiotics during pregnancy, caries status, and *S. mutans* level in saliva). Instead, another moderate quality study [22] reported no significant differences for time to first dental caries by mode of delivery (hazard ratio = 1.31 95% CI: 0.78–2.18; cesarean section is the reference group).

Discussion

According to this review, oral colonization is different between groups by mode of delivery. In 5 out of 8 studies addressing oral colonization, children born by cesarean section were less likely to harbor caries-related microorganisms as well as protective bacteria against caries and acquired caries-related microorganisms earlier when compared with vaginally delivered children. However, no consistent results were obtained for the association between mode of delivery and dental caries.

The human oral cavity harbors a large range of microorganisms, Streptococci being the most abundant bacteria detected in oral habitats of healthy individuals [32]. Although there is evidence for presence of microorganisms in placenta, umbilical cord and amniotic fluid, the first exposure of children to microorganisms occurs at birth [12]. It has been reported that the mother's vaginal microbiota provides a natural microbial exposure to the vaginally delivered newborn [13, 33]. By contrast, among children born by cesarean section, the first microbial communities reflect the human skin microbiota [13]. Therefore, differences in the mode of delivery may lead to differences in the pattern of microbial acquisition in the gut [34] and other body habitats, such as oral cavity [13, 33], which could have long-lasting health effects with clinical relevance.

Our findings are in accordance with previous research reporting higher counts of oral microorganisms among vaginally delivered children in comparison with those born by cesarean section [13, 30]. We found that vaginally delivered children are more likely to harbor *S. mutans* and *S. salivarius* which are caries-related microorganisms, but also *S. sanguinis* and *S. gordonii* considered protective bacteria against caries. However, we also observed that such differences are not consistent across studies.

Infant's oral colonization could be influenced by other factors beyond the mode of delivery. Previous research showed the influence of perinatal factors, such as prolonged rupture of membranes [35], maternal antibiotic treatment [35], and maternal sexually transmitted disease experience [14], on the establishment of oral microflora. Also, oral health behaviors including the frequency of eating sweets and toothbrushing [28, 29, 36, 37], bottle feeding and_breastfeeding [23, 28], including duration of breastfeeding [38], have been reported as determinants of oral levels of *S. mutans*. In addition, the parent's socioeconomic status [28, 37] has been associated with differences in early oral colonization by *S. mutans.* High levels of maternal salivary mutans streptococci have been also related to an increase in the risk of ECC [39]. Another issue that has been reported refers to the differences in the breast milk microbiota according to the mode of delivery, which will have an impact on early oral colonization of breastfed children [35, 40–42]. This large set of factors could explain why the association between mode of delivery and oral colonization by caries-related microorganisms and by protective microorganism against caries is not consistent across studies. Indeed, there are multiple factors that interact over time in order to determine the establishment of oral microflora. Large differences exist between studies with regard to factors other than the mode of delivery which could interact in different ways to determine oral microflora among children. This means that we should not exclude a potential role of the mode of delivery in the establishment of caries-related microorganisms and protective microorganisms against caries. Moreover, the level of mutans streptococci is a strong indicator of ECC [5]. Therefore, all factors related to oral colonization other than the mode of delivery will have an impact on the prevalence of dental caries among children.

There is a strong limitation to this review. There are few studies reporting prevalence of dental caries, prevalence of caries-related microorganisms, or prevalence of protective microorganisms against dental caries according to mode of delivery. However, to the best of our knowledge this is the first systematic review providing results on the influence of the mode of delivery on such oral health indicators among children.

In summary, according to the results of our systematic review, mode of delivery seems to shape early oral colonization but other factors could modify its effect. Further research should be conducted to give insights on multiple interactions between factors in order to disen-

tangle the role of mode of delivery from the influence of other factors on the oral colonization by caries-related microorganisms and dental caries. Professionals should be able to identify children at high risk for dental caries in providing anticipatory guidance to families. Evidence-based policies and practice are essential for dental care quality and are important for highlighting research needed in pediatric dental health [1]. Such an approach will have long-term effects on oral health with positive outcomes along life cycle, including an increase in oral health-related quality of life among older people [43].

Disclosure Statement

Authors declare no conflict of interest.

Author Contributions

C.A. and C.T. conceived the study. C.T. and C.A. conducted the systematic search of the relevant literature. All authors contributed to the review of citations and retrieved relevant information from selected articles. All authors contributed to the interpretation of results, commented on drafts and approved the final version.

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