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Risk factors for developmental defects of enamel in children from southeastern Brazil

Caio L. B. Reis,[1,2] Mariane C. F. Barbosa,[3] Daniela C. de Lima,[2] João A. Brancher,[4] Célia M. C. F. Lopes,[5] Flares Baratto-Filho,[5] Erika C. Küchler[1] and Daniela S. B. de Oliveira[2]

[1]Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil; [2]Department of Clinic and Surgery, School of Dentistry, Federal University of Alfenas, Brazil; [3]Department of Child and Adolescent Health, School of Dentistry, Federal University of Minas Gerais, Brazil; [4]School of Life Sciences, Pontificia Universidade Catolica do Parana, Brazil; [5]Department of Dentistry, University of the Region of Joinville - Univille, Joinville/SC, Brazil.

Introduction: Developmental Defects of Enamel (DDEs) comprise qualitative and/or quantitative changes to the enamel during amelogenesis. The aetiology of DDE remains inconclusive. ***Aim***: To determine the association of pre, peri, and postnatal factors with the presence of DDE. ***Design***: Cross-sectional study with 353 children (8 to 11 years-old) in a Brazilian town. ***Methods***: One calibrated dentist assessed DDE using the Developmental Defects of Enamel Index and a questionnaire collected medical and sociodemographic data. ***Main outcomes***: Children with at least one type of DDE were categorized into the DDE group. Subtypes of DDE were also recorded. ***Results***: 63.1% of children had at least one type of DDE. Diffuse opacity was present in 36.7%, demarcated opacity in 14.8%, and hypoplasia in 5.83% of the children. In multivariate analysis, demarcated opacities and hypoplasia were associated with birth weight < 2500g (OR = 4.82; 95% CI 1.23-1.95). ***Conclusion***: Low birth weight predicted DDE.

Keywords*: Growth and Development, Dental Enamel Hypoplasia, teeth abnormalities, Tooth Hypomineralization, Odontogenesis Prenatal Injuries, Neonatal Diseases*

Introduction

Developmental Defects of Enamel (DDEs) occur due to alterations in one or more of the three stages of amelogenesis (secretory, calcification, and maturation) and manifest as two major alterations: Hypoplasia and/or Hypomineralization. Hypoplasia is characterized by defective enamel formation in the secretory stage, resulting in loss of structure and reduced enamel thickness (Vargas-Ferreira *et al.*, 2018). Defects during calcification or maturation affect only translucency, with the thickness and surface of the enamel remaining regular. These lesions are known as hypomineralization defects and may manifest as demarcated or diffuse opacities. Demarcated opacity is a confined opaque area in enamel, whereas diffuse opacity is continuously distributed with varying degrees of translucency (Massignan *et al*., 2016).

Amelogenesis, is a complex and sensitive process that begins in the uterine period and extends to early childhood (Masterson *et al*., 2018). DDEs can be influenced by gene, local and/or systemic factors. Prenatal and perinatal factors, such as cigarette smoking and maternal health problems during pregnancy and premature and underweight birth have been associated with greater risk of DDEs (Corrêa-Faria *et al*., 2013; Cortines *et al*., 2019). Health problems such as asthma, urinary tract infections, gastrointestinal disturbances, and diphtheria during the first three years of postnatal life are also associated with a higher risk (Wong *et al*., 2014). Although many studies in different populations have investigated prenatal, perinatal, and postnatal factors in DDE, the results for some factors, such as maternal age, medications and prenatal care remain inconclusive (Masumo *et al.,* 2013). Thus, the aim of this study was to determine the associations between DDEs and pre-, peri-, and postnatal risk factors in a Brazilian population.

Method

The STROBE guideline was followed to inform the design and conduct of the study. This study was approved by the local Human Research Ethics Committee (HREC), protocol number 78568217.7.0000.5142. Written consent was obtained from the parents through an Informed Consent Form, and an assent term form was used for the children (appropriate for their age).

The available population for this cross-sectional study was children enrolled in public schools in Alfenas, Minas Gerais State, in southeastern Brazil. Alfenas is a medium-sized city of 73,774 inhabitants, mainly composed of European and African descendants (Brazil, 2010). The public water supply has controlled fluoride adjustment (Reis *et al*., 2020). A sample size calculation (α= 0.05; β= 0.80%; Cohen's *d* for an effect size of 0.98 [Mastora *et al*., 2017]) predicted a minimum of 276 children (http://clincalc.com; https://www.psychometrica.de/effect_size.html). A sample of all children enrolled in four schools was anticipated to exceed this target. One school was

Correspondence to: Prof. Daniela Silva Barroso de Oliveira Email: barrosodaniela@hotmail.com

selected at random from each of four different regions of the city. This sample was previously described in Reis et al. (2020). Children of both genders (8 to 11 years old) were sampled, irrespective of racial or ethnic origin. The exclusion criteria were individuals who were biologically related to a previous participant (to avoid a cluster of children with similar genetic backgrounds), those with dental prostheses, orthodontic or orthopedic appliance, severe facial or dental anomalies, carious lesion with extensive coronary destruction, systemic disorders with cognitive or behavioral problems, syndromes or those who reported a history of trauma to their primary dentition.

Medical and sociodemographic data were collected from February to May 2018, using a validated self-complete questionnaire. The questionnaire was given to parents/guardians to completed at home and enquired about sociodemographic data, medical history during the prenatal period (prenatal care, health problems during pregnancy, alcohol and cigarette consumption during pregnancy, complications at birth, use of vitamin supplements, calcium or medicines) and peri- and postnatal periods - the first three years of the child's life (premature birth, type of delivery, childbirth complications, health problems and use of medications). Self-care included use of dental floss, toothbrushing before bed and frequency of brushing per day.

DDEs were diagnosed using the Developmental Defect Enamel Index (FDI, 1992). To standardize the diagnoses, a single dentist was trained and calibrated. The dentist then examined 45 children on two occasions one week apart. Cohen's Kappa for the reliability of DDE diagnoses was 0.87, indicating near perfect reliability. Clinical examinations started after calibration, and participants in the calibration were not included in the final sample). Children were examined at school under natural light using tongue depressors, cotton wool rolls, gauze, standard mouth mirrors and ball-ended explorers, according to WHO guidelines.

DDE were categorised by type (marked or diffuse opacity and hypoplasia) and the extent of the alterations: up to 1/3 (Type 1), from 1/3 to 2/3 (Type 2), and greater than 2/3 (Type 3) of the surface of the dental crown. Single diffuse abnormalities were considered as present if they were more than 1mm in diameter. Smaller lesions were classified as "normal".

Children were classified into two groups: with DDE of any type or extent in at least one permanent or deciduous tooth (DDE Group) and without enamel defects (Control).

The results were analysed using the software Epi Info 7. The dependent variables were the presence or absence of DDE and the DDE subgroups. The independent variables were the medical and sociodemographic factors. Chi-square or Fisher exact tests were used to compare frequencies among groups. Unadjusted and adjusted model logistic regressions were performed and odds ratios (OR) and 95% confidence intervals (CI) were estimated. The statistical significance level adopted was 0.05.

Results

Among 353 included children, 51.84% were girls and 48.16% boys. Almost two thirds had a DDE (63.17%), most (57.4%) of whom had only one type, while 42.6% had two or three types. Diffuse opacity was the most common form (36.8%) (Table 1). DDE was present in both arches in 55.2% of children, 31.4% had DDE only in the maxilla 13.4% only in the mandible. Incisors and canines were affected in 44.85%, premolars and molars in 13.9%. DDE affected all types of teeth in 41.3% of the sample.

Less than 1/3 of the clinical crown was affected (Type 1) in 68.6% of children have. Type 2 DDE was present in 6.7%. Only one child had Type 3 DDE. Almost one quarter (24.2%) of children had a combination of DDE types.

Table 2 shows the associations between DDE with pre, peri and postnatal factors. In bivariate analysis, advanced maternal age (≥ 35 years) was associated with the presence of DDE but in the adjusted logistic regression analysis (Table 3), only low birth weight (< 2500g) was associated with the frequency of demarcated opacities and hypoplasia (OR, 4.82; 95% CI, 1.23-18.95). Bivariate analyses for each type of DDE are available at https://drive.google.com/drive/folders/17OUiFRGMx2ky_N5FIGrXR6xFbQw3MBPy?usp=sharing).

Some factors (Vitamins during pregnancy and illness or medications before the age of three) were divided into subgroups for analyses, but were not associated with DDE. Self-report of use of dental floss, brush teeth before sleep and how often brush teeth per day were also not associated with DDE (data not shown).

Discussion

A recent meta-analysis review pointed out that more studies should be performed to improve the evidence about the risk factors for DDE, due the low quality of the previous studies (Fatturi *et al*., 2019). The roles of some medical and social factors, such as maternal age, vitamins during pregnancy and medications during childhood have not yet been fully explored in the aetiology of DDE.

The prevalence of DDE in this sample was high, but similar to that of previous Brazilian studies (Vargas-Ferreira *et al*., 2018; Ruschel *et al*., 2019). Social factors such as low quality of life, poor access to health care and nutritional problems, common in developing countries as well as Brazil, are related to the high prevalence of DDE (Corrêa-Faria *et al*., 2013). Many children (42.6%) had more than one type of DDE. This suggests that the children experienced constant exposure to one or more factors, because each type develops at a different time during infancy.

Table 1. Distribution of DDEs in 353 children

	%
DDE Present	63.17
DDE Absent	36.83
Types of DDEs	
Demarcated Opacities	14.80
Diffuse opacities	36.77
Hypoplasia	5.83
Demarcated and diffuse opacities	24.21
Demarcated opacities and hypoplasia	10.76
Diffuse opacities and hypoplasia	0.90
Combination of all three defects	6.73

Table 2. Medical factors and the presence of DDE in 353 children

	No (n = 130) %	*Yes (n = 223) %*	*p (Chi sq.)*
Prenatal care (n = 351)			
Yes	98.4	98.4	0.858
No	1.5	1.6	
Maternal age (n=329)			
< 34 years	96.5	90.1	0.033
≥ 35 years	3.5	9.9	
Health problem during pregnancy (n=350)			
Yes	14.0	13.2	0.825
No	86.0	86.8	
Smoked (n=351)			
Yes	18.6	19.8	0.781
No	81.4	80.2	
Alcoholic drinks (n=349)			
Yes	9.3	9.5	0.968
No	90.7	90.5	
Vitamins during pregnancy (n=348)			
Yes	71.1	67.7	0.512
No	28.9	32.3	
Complicated delivery (n=344)			
Yes	8.67	7.8	0.786
No	91.3	92.2	
Natural	44.8	47.2	0.661
Caesarean	55.2	52.8	
Birth weight (g) (n=312)			
< 2500	12.8	12.8	>0.99
≥ 2500	87.2	87.2	
Premature birth (n=332)			
Yes	11.7	10.4	0.959
No	89.3	89.6	
Breastfeeding (n=351)			
Yes	91.8	78.8	0.542
No	8.2	21.2	
Illness in first three years (n=347)			
Yes	24.8	30.3	0.274
No	75.2	69.7	
Medication in first three years (n=331)			
Yes	19.8	25.2	0.262
No	80.2	74.8	

Table 3. Logistic Regression for predictors of demarcated opacities and hypoplasia in 353 children.

	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)
Birthweight ≥ 2500	Reference	
Birthweight < 2500	4.21(1.41-12.61)	4.82 (1.23-18.95)

* Variables at $p < 0.05$ in chi square analysis were tested. Prenatal care and maternal age were not associated in logistic regression
¶ Adjusted for other perinatal factors (Complicated delivery, type of delivery and prematurity)

Corroborating Corrêa-Faria et al. (2013), Masumo et al. (2013), and Cortines et al. (2019) we found an association between low birth weight and both demarcated opacities and hypoplasia. Low birth weight may cause developmental defects in several ways. First, it predisposes to perinatal factors including systemic conditions such as anemia and hypocalcemia. Low birthweight also reflects poor nutritional status during pregnancy. The immaturity of the respiratory system and gastrointestinal tract in underweight children may restrict the metabolism of nutrients necessary for the normal development of the teeth, and may require hospitalisation (Jacobsen *et al*., 2014). Some studies only associate low birth weight with hypoplasia (Masumo *et al*., 2013). However, the disturbances of calcium metabolism in low birth weight children can affect both matrix development and mineralization, increasing susceptibility to hypoplasia and opacities (Jacobsen *et al*., 2014).

Alcoholic drinks and smoking were not associated with DDE, as was the case with other Brazilian studies (Corrêa-Faria *et al.*, 2013, Vargas-Ferreira *et al*., 2018). Inference about alcoholic drinks and smoking is difficult because mothers may feel uncomfortable reporting these behaviours, and may omit answering them.

To the best of our knowledge, this study was the first to assess vitamin intake during pregnancy as a risk factor to DDE. However, we did not find an association. There is insufficient evidence available on the effects of vitamins on dental development, which precludes a more comprehensive discussion, thus, further studies should be conducted.

In Brazil, prenatal or antenatal care includes general information to women about how to have a safe pregnancy (Viellas *et al*., 2014). Pregnant women who do not perform prenatal care may be more susceptible to external factors that might alter normal tooth formation in their baby (Salanitri and Seow, 2013). However, prenatal care was not associated with DDE in multivariate analysis. Data in the literature regarding the association of premature birth and DDE seem to point to an association between these factors. However, prematurity can be a confounding factor for the need for neonatal intubation, which may cause trauma and thus be associated with developmental defects of the teeth (Tourino *et al*., 2016). We did not find associations between prematurity or prenatal factors and DDE. Mastora et al. (2017) found more enamel defects among children with asthma and suggested that using bronchodilators, antihistamines, and corticosteroids may cause DDE. We did not find an association between DDE and medication use in early years. Further studies could clarify this factor.

Given the complexity of amelogenesis, it may be that the effects of any one risk factor are relatively small, so that very large samples are required to identify them. One other limitation of this study was that the guardians completed the questionnaire at home. Despite accelerating the process of epidemiological surveys, the use of questionnaires may restrict the collection of detailed information such as type of vitamins or other medications or the history of diseases.

This study incorporated potential risk factors that have received little attention, including prenatal care, maternal age and vitamins during pregnancy. Other studies should be performed in other populations to improve the evidence relating to these risk factors and to explore other possible factors.

Conclusion

This study investigated many independent variables as predictors of DDE in 353 children in Brazil. Low birth weight was associated with the presence DDE.

Conflict of interest

None.

Acknowledgments

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