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ORIGINAL ARTICLE

Syphilis and Urogenital Diseases during Pregnancy and Developmental Defects of Enamel: A Brazilian Prenatal Cohort (BRISA)

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ABSTRACT

Objective: To evaluate the effect of syphilis and urogenital diseases (SUD) during pregnancy on developmental defects of enamel (DDE) using causal inference models. **Material and Methods:** This study is a prospective cohort – the Brazilian Ribeirão Preto and São Luís Cohort Study (BRISA) – including 865 mother-child dyads, evaluated in three moments: prenatal care (22nd and 25th weeks of gestational age); baby birth; and between 12.3-36 months of age. The outcome was assessed according to the modified DDE index. The exposition, SUD, comprised at least one of the following infections: bacterial vaginosis, urinary tract infection, and syphilis. The covariables included in the theoretical model were socioeconomic situation (SES), low birth weight, mother's age, number of prenatal care visits (PCV), hypertension, diabetes, medication use during pregnancy, and child's age. Based on the proposed directed acyclic graph (DAG), SES and the number of PCV were the minimal set of covariables for the adjusted model. The effects were estimated by causal inference using a marginal structural model (Average Treatment Effect - ATE coefficients). **Results:** SUD did not interfere in the incidence of DDE (ATE: -0.92; CI95%: -0.23-0.49; p=0.202). **Conclusion:** SUD during pregnancy does not have a causal effect on DDE on primary dentition. Another possibility is that other infections not included in the model may have confounded the association, biasing toward the null hypothesis.

Keywords: Developmental Defects of Enamel; Epidemiologic Methods; Pregnant People; Infections.

Introduction

The Developmental Origins of Health and Disease (DOHAD) approach seeks to understand underlying mechanisms of childhood health, therefore identifying alternative measures of early childhood experience in addition to birth weight and stunting, particularly those that capture the source and period of exposure in early childhood, such as developmental defects of enamel (DDE) [1]. DDEs are important stress markers arising from the disruption of ameloblastic activity during enamel matrix secretion and mineralization [2]. Insults during the prenatal, natal, and postnatal periods can permanently impair the primary enamel, providing a chronological indicator of stressful events [3].

The etiology of DDE has not been fully elucidated, but it has been associated with adverse birth outcomes, such as low birth weight (LBW) [4,5], preterm birth [4,5], and intrauterine growth restriction [6]. Besides, socioeconomic factors [7], tobacco use [3], growth hormone deficiency [8], gestational diabetes [9], hypertension [10], use of antiepileptics [11], malnutrition [12] and alcohol consumption [13] have been considered risk factors for DDE in deciduous dentition. History of infectious and congenital diseases in children has been suggested as a predisposing factor for DDE in deciduous and permanent dentitions [14,15]. Enamel hypoplasia has been described as one of the oral changes in congenital syphilis [16,17]. It is still unclear whether urogenital diseases – bacterial vaginosis (BV) and urinary tract infection (UTI) – during pregnancy interfere with amelogenesis in babies.

The prevalence of BV in Latin America and the Caribbean is 24%, and the estimated annual global economic burden of treating symptomatic BV was US $4.8 billion [18]. Furthermore, in a systematic review with meta-analysis, the prevalence of symptomatic and asymptomatic UTIs in pregnant women was around 23.9% [19]. In Brazil, the gestational syphilis detection rate increased by approximately 53.4% between 2010 and 2020, showing an increase in the three arches, North (72.8%), Central (34.7%) and South (102.0%) and in Brazil (66.3%) [20]. Maternal infections, such as BV, UTI, and gestational syphilis, are major risk factors for LBW and related adverse birth outcomes [21]. These maternal urogenital diseases possibly increase the development of DDE in deciduous dentition.

Previous studies on the association between prenatal factors and DDE in children of mothers with known pregnancy conditions present limitations concerning study design and control of confounding bias. That said, marginal structural models are a helpful tool to control confounder bias based on counterfactual logic [22]. The tool balances the confounders across the exposure, thus providing a better approach for estimating causal effects. Therefore, we aim to evaluate the effect of syphilis and urogenital diseases on DDE, estimating causal effects.

Material and Methods

Study Design, Setting and Ethics Considerations

This study is a prospective cohort (Etiologic factors of preterm birth and consequences of perinatal factors on child health: birth cohorts in two Brazilian cities – BRISA study). The reference population consisted of pregnant women who received prenatal care in public and private health services and were referred to the University Hospital of the Federal University of Maranhão in São Luís city. Children who had had dental examinations were also included in the study.

São Luís is a capital located on an island in the Northeast region, the poorest in the country. Its Human Development Index (HDI) was 0.768 in 2010, ranking 249th in Brazil, while per capita income was approximately

$10,475.35. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

The study was approved by the local Research Ethics Committee (Proc. N. 4771/2008-30) on April 8, 2009. All participants signed an informed consent form. Participants' anonymity and data confidentiality were guaranteed, as were the principles of beneficence and non-maleficence.

Study Sample

Pregnant women with ultrasonography between 22nd and 25th weeks of gestational age were included in the study. The recruitment occurred between February/2010 and November/2011, involving 1,447 pregnant women (baseline or T0). Of these, 66 did not show up to follow-up visits or did not answer the questionnaires. A total of 1,381 (93.94%) were followed up at the time of the baby's birth (T1). Subsequently, 1,160 children (80.2%) were re-evaluated, but 865 underwent dental examinations (T2). This sample of 865 dyads (mother-infant).

Data Collection and Study Variables

Face-to-face interviews and self-administered questionnaires were carried out with the children's mothers at baseline, 1st, and 2nd follow-up. Data collection from medical records and children's dental examinations were also performed. Previously trained health professionals administered the questionnaires, and dental surgeons performed dental examinations on children.

Exposition

We collected data regarding the following systemic infections during pregnancy: syphilis, VB, and UTI. Maternal bacterial infections were determined based on three questions: Did you have syphilis during pregnancy diagnosed by a doctor or nurse? Did you have any urinary tract infections during your current pregnancy that were diagnosed by a doctor or nurse? Did you have any bacterial vaginosis during pregnancy?

Outcome

Each child was examined in a portable dental chair, under artificial light, after tooth drying by air jets, using a WHO-621 periodontal probe and a mouth mirror (Hu-Friedy Mfg. Co., Chicago, IL, USA), sterilized previously, and packaged individually. Five trained examiners conducted the procedure to diagnose DDE (Kappa inter-examiner = 0.82). Diagnosis of DDE was performed according to a modified version of the Index proposed by the World Dental Federation [23]. Once the DDE was identified, the tooth was classified according to opacity, hypoplasia, and other defects. We considered as uterine origin all defects present in the occlusal/incisal third [6,24]. The dependent variable was the number of teeth with DDE.

Covariates

Maternal age (in years), Child's age (in months), economic class according to the Brazilian Criteria of Economic Classification - BCEC (In Portuguese: *Critério de Classificação Econômica Brasil* - CCEB) [25], categorized as A/B (best), C and D/E (worst); hypertension during pregnancy (yes or no); diabetes during pregnancy; use of medication during pregnancy (yes or no); number of prenatal care visits (0-3, 4-5 and six or more) and Child birth weight was categorized as low weight <2500 g and adequate weight ≥ 2,500 g [26].

Theoretical Model Based on Direct Acyclic Graphs (DAGs)

The proposed theoretical model was constructed to analyze the association between syphilis and urogenital diseases during pregnancy and the outcome number of teeth with DDE. SES, mother's age and prenatal care were common antecedents, exerting their effect on the exposure, urogenital diseases during pregnancy [27-30], and on the outcome, DDE [7,31,32]. The mother's age could also be associated with hypertension, gestational diabetes and LBW [33-35]. The LBW results from either preterm birth - birth at <37 weeks completed gestation - or fetal growth restriction, often resulting in a small for gestational age infant - less than the 10th centile of weight to gestational age [21]. Almost all variables in the theoretical model would affect LBW [36]. The covariates hypertension [10], diabetes [9], use of medication during pregnancy [11,37], child's age [24] and LBW [24] explained the DDE (Figure 1).

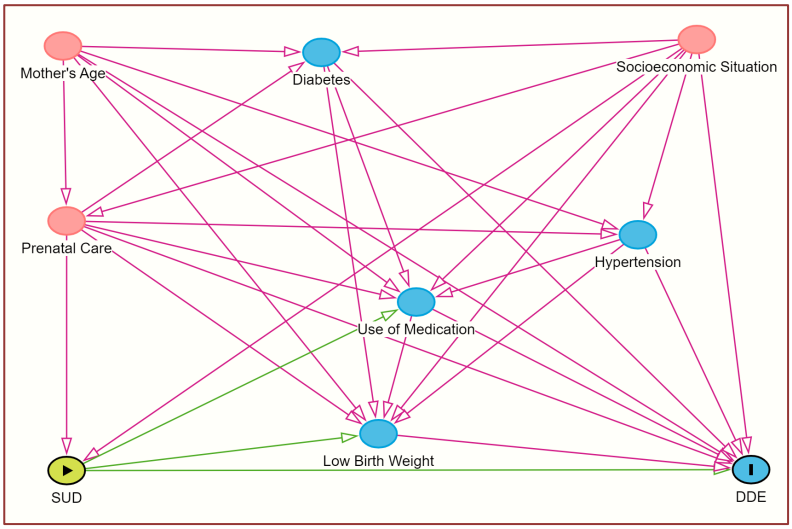

Figure 1. Theoretical model based on DAGs of the association between urogenital diseases during pregnancy and developmental defects of enamel in children.

Statistical Analysis

The DAG was generated using the DAGitty software, version 3.0.15. The DAGs are causal diagrams that allow the researcher to visualize the study question, establish causal assumptions between variables, and define a minimum set of variables to estimate the effect of exposure on the outcome, controlling the confounding effects and avoiding unnecessary adjustments. The indication of these variables for minimum adjustment occurred based on the back-door criterion, which considers the need for adjustment for a variable that is a common cause to other two variables in a particular causal pathway and does not indicate adjustment for a collider variable, one which is caused by other two variables, in the same causal path [38,39]. The variables considered as the minimum adjustment for this model were socioeconomic status and number of prenatal visits (Figure 1).

The assumptions about causal inference are as follows: the intervention must be well defined; there must be interchangeability between the exposed and unexposed groups (measured by the balance of observed variables); there must be a single treatment (exposition) version (DDE is a single condition); there must be observations in all subgroups (positivity); and there must be no contamination. According to the counterfactual approach, the final sample was inverse probability weighted for treatment (DDE), considering the minimal set of confounding variables by the effects of *ipwra* routine. Balancing between groups was checked to assess whether conditional permutability could be assumed by the difference in standardized means and variance ratio between

groups [38,39]. The optimal difference in standardized means is zero (where < 0.2 is acceptable), and the optimal variance ratio is 1 (values from 0.8 to 1.2 are acceptable) [38,39]. All analyses were performed with STATA software (version 16.0, Stata Corp., College Station, TX, USA). The effects were estimated by causal inference using a marginal structural model. Average Treatment Effect (ATE) coefficients and 95% confidence intervals (95% CIs) were calculated using a 0.05 significance level.

Results

The prevalence of intrauterine DDE was 9.88%, so 143 children with at least one tooth were affected. The mean of teeth with intrauterine DDE-IU was 0.20 (±1.02), ranging from zero to six teeth. Most pregnant women belonged to socioeconomic class C (65.14%), and most reported bacterial infections during pregnancy (63.28%) (Table 1). The mean maternal age was 25.90 years (range of 14 to 45 years, with a median of 22.00-29.00 and Q1-Q3 = 22.00-29.00), and the mean age of the children was 16.37 months (range of 12.3 to 36 months, with a median of 15.63 and Q1-Q3 = 14.72-17.20).

Table 1. Characterization of the population of the study, according to the incidence of DDE-iu BRISA.

Variables	N	%
Dental Enamel Defects		
Yes	74	8.56
No	791	91.44
Number of prenatal care visits		
≤ 3	11	1.45
4-5	106	13.98
6 or more visits	641	84.56
Brazilian Criteria of Economic Classification		
A-B	124	15.01
C	580	70.22
D-E	122	14.77
Low birth weight		
≥ 2500 g.	818	94.56
< 2500 g.	47	5.44
Diabetes		
No	828	95.72
Yes	37	4.28
Systemic Infections		
Yes	533	61.61
Não	332	38.39

Balance statistics showed exchangeability between the groups regarding the observed variables included in the minimum set of adjustments for confounding (Table 2).

Table 2. Balance of variables in the exposed and non-exposed groups before and after inverse probability of selection weighting of the BRISA Birth Cohort.

Variables	Standardized Differences		Variance Ratio	
	Raw	Weighted	Raw	Weighted
ABEP				
A/B	Reference			
C	0.1265782	0.1261173	0.9056446	0.9051369
D/E	-0.0644118	-0.079772	0.8859324	0.859287
Number of Prenatal Care Visits				
6 or more visits	Reference			
4-5	-0.0063192	0.003446	0.9868934	1.007729
≤ 3	-0.0121296	-0.0052091	0.9144537	0.9620014

Syphilis and urogenital diseases do not interfere with DDE incidence (ATE= -0.92; CI95% = -0.23 - 0.49; p=0.202) (Table 3).

Table 3. Estimating the causal effect of systemic infections on dental enamel defects of the BRISA Birth Cohort.

	Coefficient 95%	CI 95%	p-value*
Infection Diseases	0.025332	-0.1106689 to 0.1613328	0.715

CI 95%: Confidence Intervals; *p-value < 0.05.

Discussion

In the present study, syphilis and urogenital diseases were not associated with DDE in the estimation carried out with the marginal structural model. The literature mentions that fever, systemic inflammation, bacterial and viral infections [3,15,31], and medication use – during pregnancy or after childbirth [11,37] – may interfere with developing DDE. Bacterial infections during pregnancy, such as syphilis [16,17]. However, there is still little evidence about the role of other maternal infections in the origin of DDE [40]. In a Brazilian study with 665 schoolchildren, UTI and vaginal discharge were not associated with DDE, in agreement with the results of our study [31]. The variability in children's age and the diagnostic criteria for exposure and outcome possibly contribute to the differences in the literature.

The prevalence of pregnant women in this sample with six or more consultations during prenatal care was 84.56%, increasing the possibility of interference with the treatment of maternal bacterial infections during our study. The survey "Birth in Brazil", carried out in 2013, showed that more than 90% of pregnant women were tested for HIV and 77.9% for syphilis [41], reinforcing that women with a bacterial infection diagnosed during prenatal care were possibly treated and monitored, reflecting advances in prenatal care qualifications and improved maternal and child health in Brazil.

The inclusion of children with 12.3 months in this study may have contributed to the low prevalence of DDE. A Brazilian study on dental chronology composed of four Brazilian cohorts observed that at 12 months of age, 25% of children had four or fewer erupted teeth, 75% had seven or fewer, and 95% had 11 or fewer [42]. Therefore, we recognize the divergences in the literature regarding the chronology of tooth eruption, prevalence, and distribution of teeth most affected by DDE in this study [24]. However, the central and lateral incisors and first molars have already been identified as the teeth with the highest incidence of DDE in previous studies [43,44]. In addition, no reports in the literature show that primary second molars are more affected by DDE [45,46].

Methodological differences in the diagnosis of DDE, especially the broad age range of the children included in the studies, may interfere with the results. A distinctive incremental line (neonatal line) observed at childbirth allows for distinguishing between prenatal and postnatal enamel formation, determining the timing of these biological changes; however, most studies have not assessed the timing of enamel formation [6]. Therefore, it is not possible to determine from other studies whether DDE emerged in the intrauterine or postnatal period. However, from the 13th week of pregnancy, the primary upper central incisors develop. In contrast, the other primary teeth begin to develop from the 15th week with a phase change of a few weeks each other [46]. Crown formation and maturation completion occur in the perinatal and postnatal period, around 9-11 months since birth [47].

The limitations of our study were the infectious diseases during pregnancy were self-reported, thus being subjected to memory bias and misestimation, and some variables not included in the model, such as the

presence of other bacterial and viral infections, anemia, and maternal nutritional deficiencies. However, we asked for infections occurring during pregnancy; thus, at a time still very close to the interview, reducing the possibility of memory bias. Furthermore, we only consider the presence of disease when diagnosed by a healthcare professional, which minimizes this problem. In addition, this sample is representative, thus helping to reduce possible confounding bias.

This study is the first to assess intrauterine DDE by using causal inference. In addition, we proposed the set of measurable covariates depicted in a DAG to minimize the risk of inaccurate measurement of confounders. All other assumptions of exchangeability, positivity and well-defined exposures were satisfied, allowing the marginal structural model to be used for the causal analysis of observational data. Moreover, the selection of intrauterine DDE as an outcome allows more accurate analyses of the effects of exposure during the gestational period. The outcome was regarded as a discrete variable, increasing the statistical power, whereas most investigations consider it binary. Finally, the objective and standardized analysis of intrauterine DDE allowed a more consistent investigation of new etiologic hypotheses.

Conclusion

We did not observe a causal effect between DDE and bacterial infections during pregnancy among children using graphical and counterfactual approaches to minimize confounding and selection bias. However, it is important to improve the quality of prenatal care, reduce the prevalence of systemic maternal infections and study the etiological factors of DDE.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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