The Association Between MIH and Early Environmental Exposures

Thesis

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By

Erin Bibber

Graduate Program in Dentistry

The Ohio State University

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Thesis Committee

Daniel Claman, DDS, Advisor

Paul Casamassimo, DDS, MS

Kim Hammersmith, DDS, MPH, MS

Janice Townsend, DDS, MS

Ashok Kumar, DDS, MS

Jin Peng, MD, MS, PhD

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Abstract

Purpose: To determine an etiological association between the presence and severity of Molar Incisor Hypomineralization (MIH) and environmental exposures (pre-, peri-, or postnatal), early childhood illness, antibiotic use, systemic disease, race/ethnicity, or socioeconomic status.

Methods: This was a hospital-based, nested case-control study of children 6-17 years old identified as having MIH via clinical exam. MIH severity was rated using the European Academy of Pediatric Dentistry (EAPD) scale. A retrospective chart review of subjects identified as having MIH, along with their age-matched controls without a diagnosis of MIH, examined the potential relationships between environmental and social factors and MIH diagnosis.

Results: The study cohort was analyzed using logistic regression for associations between demographic variables and MIH. MIH was not significantly associated with age, race, language, ethnicity, or insurance type. Patients who had the DTaP Vaccine were less likely to have MIH (Odds ratio = 0.3, P-value = 0.01) and severe MIH (Odds Ratio=0.2, P-value=0.0003) than patients who did not have DTAP vaccine. Statistical analysis showed near significant associations between histories of otitis media, passive smoke exposure, and asthma for patients with an increased incidence for mild MIH.

Conclusions: Molar Incisor Hypomineralization remains a multidimensional, multifactorial diagnosis with several potential etiological associations. The DTaP vaccination status may be a variable of interest for future MIH studies. Prospective studies with increased sample size and consistent medical record information are needed to further evaluate etiological associations.

Dedication

This document is dedicated to my family, who has supported me throughout my education, and my research advisors for their guidance and expertise.

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Vita

June 2011……...……Shepherd Hill High School, MA

May 2015……BS Neuroscience, University of New England Biddeford, ME

May 2020……DMD, The University of Connecticut School of Dental Medicine, CT

July 2020 to Present……..Resident, Division of Pediatric Dentistry

The Ohio State University and Nationwide Children's Hospital, OH

Fields of Study

Major Field: Dentistry

Table of Contents

List of Tables

List of Figures:

Chapter 1: Introduction

Molar Incisor Hypomineralization (MIH) was first defined in 2001 by Weerheijm et. al. as qualitative, demarcated developmental defects of systemic origin that affect the enamel of one or more first permanent molars (FPMs) with or without incisor involvement (1). MIH presents clinically as demarcated opacities that range in color from yellow to brown (2,3). The soft, porous enamel of teeth involved often undergoes post-eruptive breakdown resulting in atypical caries or complete coronal distortion (2,3). The prevalence of MIH ranges between 4 and 25% (1,4, 5), and seems to differ by geographical region (1,2,6).

These enamel defects pose significant clinical management challenges for patients, caregivers, and dental providers. The variation in clinical appearance allows for a range of treatment planning options, including but not limited to preventive measures, restorations, and extractions with subsequent orthodontic or prosthetic management (6). Additionally, children with MIH may have elevated symptoms of pain and hypersensitivity as a result of dentin exposure, leading to pulpal inflammation and difficulty achieving adequate local anesthesia (4). Due to this hypersensitivity, children often become fearful of oral interventions with an elevated likelihood of developing dental anxiety (1).

Although many authors have agreed upon its multifactorial pathogenesis and acknowledged its genetic components, the etiology of MIH remains largely unclear (4,5,7). Etiological associations with systemic conditions and environmental insults throughout the first three or four years of life have been suggested (7, 8). Recent literature has reported the etiology of MIH to be associated with early childhood illness, as well as prenatal, perinatal, and postnatal factors (3, 5, 7). Fatturi et. al reports that maternal illness, psychological stress, cesarean delivery, delivery complications, respiratory diseases, and the occurrence of fever in a child's first five years of life

have been shown to increase MIH incidence (9). According to Sadashivamurthy et.al, common medical conditions or diseases in the first three years of life such as asthma, otitis media, varicella, measles, and rubella have been associated with MIH (10). Other systemic illnesses thought to increase MIH incidence include cystic fibrosis, epilepsy, repaired cleft lip and palate, and nutritional deficiencies (10).

Medications taken in the first four years of life have also been implicated (5). Serna et. al. conducted a meta-analysis investigating medications such as antibiotics, antiepileptics, immunosuppressant medications for chemotherapy, and medications used for asthma such as corticosteroids and bronchodilators. Studies found mixed results regarding a significant association between medication use prior to the age of three and an increased incidence of MIH (1,9). Several studies have postulated the use of antibiotics, penicillin specifically, could be associated with increased prevalence of MIH, however it has been difficult to distinguish whether the association with MIH has been related to antibiotic use or the illness itself (1,7,9,10).

The extent of hypomineralization complicates the restorability and long-term prognosis of affected teeth, therefore proposed treatment modalities may be dependent upon the severity of MIH. Lydiakis et. al confirms that severity should be recorded as mild or severe in order to help the clinician decide on an appropriate treatment plan (3). According to Elhennway et. al, the broad spectrum of treatment modalities includes management of hypersensitivity or pain, restorative treatments, and extraction with or without orthodontic intervention (4). To make informed clinical decisions, the provider must consider the dental age of the patient, parental expectations, esthetics, and cost-effectiveness, as well as understand the suitability of treatment options proposed for individual patients (3,4).

Several limitations within the current literature challenge the confirmation of etiological associations for MIH diagnoses. Recall bias, poor diagnosis and classification, and lack of adjustment for confounding factors complicate the picture of an MIH etiology (9, 12). Most current studies are retrospective and rely heavily on parental recall (1,9). Silva et. al mentions that the recall of some aspects of maternal health during pregnancy, child illness, and medication use may be unreliable (7, 9). In addition, several studies have pointed out challenges in obtaining accurate medical records with consistent and detailed data (7, 11). It has been suggested that prospective studies with emphasis on early diagnosis are needed to clarify the factors and mechanisms behind enamel defects (1).

This nested case-control study aimed to determine etiological associations between the presence and severity of Molar Incisor Hypomineralization (MIH) and environmental exposures (pre-, peri-, or postnatal), early childhood illness, antibiotic use, systemic disease, race/ethnicity, or socioeconomic status.

Chapter 2: Methods

2.1 Protocol and Registration

This study was approved by the Human Subjects Committee of Nationwide Children's Hospital, Columbus, Ohio (IRB 00001783).

2.2 Sample and Selection Criteria

This hospital-based, nested case-control study included patients presenting to Nationwide Children's Hospital Dental Clinic for routine dental examinations. Patients aged six to 17 years old were prospectively recruited based on a clinical diagnosis of MIH documented electronically by a calibrated dentist. Patients must have had documented medical records available, including perinatal evaluation, for inclusion. Patients with amelogenesis imperfecta (AI), dentinogenesis imperfecta (DI), fluorosis, or any other condition exhibiting generalized enamel defects were excluded. Age-matched controls without an MIH diagnosis were subsequently identified and recruited for the study.

2.2 Calibration

Prior to commencement of the study, dental providers at Nationwide Children's Hospital were collectively presented with images of MIH-affected molars of varying severity for calibration. Providers were also presented with images of teeth not affected with MIH, or molars affected with other types of enamel defects, for comparison. Dental providers were responsible for initial screening for study inclusion, as participants were recruited during routine intraoral examinations.

2.3 Procedure

During examinations, clinical images of affected molars were obtained by dental providers and electronically uploaded to the electronic health record using Epic Haiku (Epic Systems

Corporation, Verona, WI). An initial data query from Epic Hyperspace was extracted using Oracle SQL developer software (Oracle, Redwood Shores, CA) to identify a preliminary number of subjects diagnosed with MIH from June 1st 2021 to April, 1st 2022. A single dental provider manually analyzed the electronic records of subjects with a clinical MIH diagnosis. Clinical photographs, in conjunction with the patients dental history, were used to affirm or deny documented MIH diagnoses, and thus, confirmed participant inclusion. MIH severity was also scored at this time using the European Academy of Pediatric Dentistry (EAPD) scale (**Figure 1)**.

Severity Grade of MIH	Definition
Mild	Demarcated enamel opacities without enamel breakdown. Occasional sensitivity to external stimuli (e.g. air), but not brushing. Mild aesthetic concenrs on discoloration.
Severe	Demarcated enamel opacities with breakdown, caries persistent/spontaneous hypersensitivity affecting function (e.g. brushing). Strong aesthetic concerns that may have socio-psychological impact.
MIH: Molar Incisor Hypomineralization, EAPD: European Academy of Pediatric Dentistry	

Figure 1: European Academy of Pediatric Dentistry (EAPD) MIH Severity Scoring

Data parameters were selected for investigation in this study using the Delphi method, and were based on a comprehensive literature review of exposures associated with a higher incidence of MIH. The following data parameters were documented for individual participants: demographic variables, medical history information (including, but not limited to, birth history and maternal data, surgical history, and medication use), dental history, and presence/severity of MIH **(Table 1**).

Table 1: Environmental and Socioeconomic Variables

Variable	Variable Description	Metric
Demographics		
Age at Visit	Age (Months)	Number
Gender	Sex - M/F	Categorical
Ethnicity	Latino/Hispanic vs. Non-Latino/Hispanic	Categorical
Language	English vs. Non-English	Categorical
Race	Black vs. White vs. Other	Categorical
Dental Insurance Type	Self-pay, Commercial, Medicaid	Categorical
Molar Incisor Hypomineralization (MIH)		
MIH Presence	Presence of MIH	Y/N
MIH Severity	Scale of Severity	0: Mild; 1: Severe
Prenatal Exposures		
Maternal Tobacco Use	History of	Y/N
Maternal Alcohol Use	History of	Y/N
Maternal Drug Use	History of	Y/N
Pregnancy Complications	History of	Y/N
Illness during Pregnancy	History of	Y/N
Perinatal Exposures		
Low Birthweight	Low birthweight (< 5 lbs, 8 oz.)	Y/N
C-section Delivery	C-section vs. vaginal delivery	Y/N
Premature Birth	premature birth (< 37 weeks)	Y/N
Postnatal Exposures		
NICU Admission	History of	Y/N
Passive Smoke Exposure	History of	Y/N
Hospital Admission	History of	Y/N
Early Childhood Illness	Early Childhood Illness (< 4 y/o)	
Asthma	History of	Y/N
Fever	History of	Y/N
Adenoiditis	History of	Y/N
Respiratory Infection	History of	Y/N
Varicella	History of	Y/N
Tonsillitis	History of	Y/N

Variable	Variable Description	Metric
Otitis Media	History of	Y/N
Medication_Use	Medication use (< 4 y/o)	
Antibiotic	History of	Y/N
NSAID	History of	Y/N
Acetaminophen	History of	Y/N
Systemic Conditions		
DTaP Vaccination	History of	Y/N
Hypoparathyroidism	History of	Y/N
Repaired cleft lip/palate	History of	Y/N
Hypocalcemia	History of	Y/N
Cystic Fibrosis	History of	Y/N
Epilepsy	History of	Y/N
Developmental Delay	History of	Y/N
Autism Spectrum Disorder	History of	Y/N

Table 1: Environmental and Socioeconomic Variables (con't)

According to the EAPD MIH Severity Scale, affected FPMs were scored 0 for mild MIH and 1 for severe MIH. Molars were classified as mild MIH if they had demarcated enamel opacities without caries, that were either planned for sealant treatment or had an existing sealant present, or did not have an existing restoration. Hypoplastic molars were characterized as severe MIH if they had demarcated opacities and an existing restoration, gross caries and/or caries documented on the patient's tooth chart, showing post-eruptive breakdown, or if they had been extracted due to non-restorability. Hypersensitivity was not included in the assessment to reduce subjectivity during assessment. A second data query to identify an age-matched control group was completed for comparison. A 2:1 ratio (No MIH:MIH) was used to increase the validity of the results.

2.4 Data Analysis

A power analysis was completed prior to data collection to determine effect size. It was determined that an effect size of 82 participants with MIH was needed to validate result significance.

Descriptive statistics were generated using frequency values. The logistic regression model was used to associate early life events and the presence of MIH. The odds ratio (OR) with a 95% confidence interval was used to evaluate associations between environmental and/or demographic variables and MIH. A p-value ≤ 0.05 was considered statistically significant.

Chapter 3: Results

3.1 Study Selection

There were 178 patients aged six to 17 years with a MIH diagnosis documented in Epic during the study period (**Figure 2)**. Of these, only 92 fit inclusion criteria. The remaining 86 patients were excluded due to undocumented clinical photographs of affected teeth, not having an affected FPM, having a localized defect of enamel that was not characteristic of MIH, or having generalized enamel defects inconsistent with MIH. Of the 92 MIH cases, 40 were characterized as mild and 52 were characterized as severe. A total of 276 patients were included in the study after combining age-matched controls (n = 184) with MIH patients (n = 92).

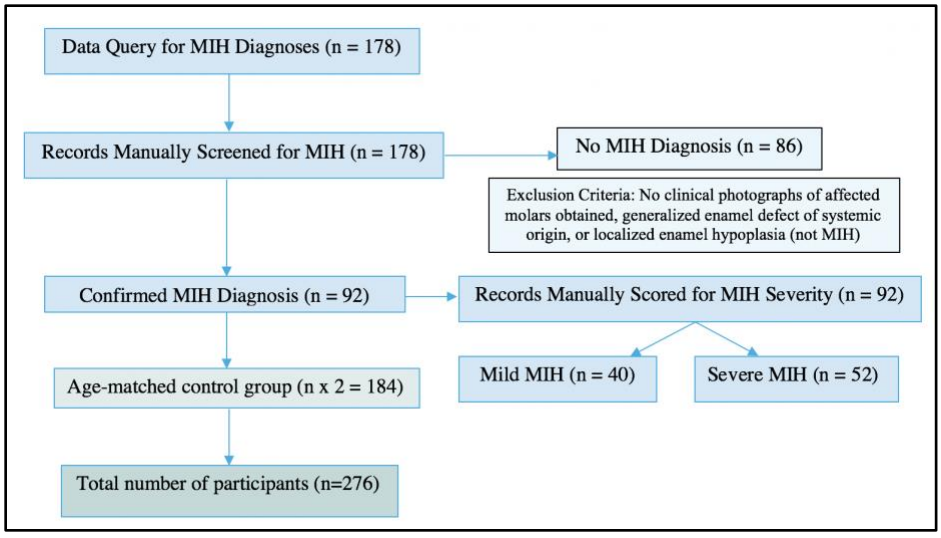

Figure 2: Inclusion/Exclusion Criteria Flow Chart

3.2 Study Characteristics

Descriptive statistics were generated for both the experimental group (MIH) and the control group (no MIH) using frequency values for each variable **(Table 2)**. The mean age of the population was 120.78 months (10.07 years). For the experimental group, gender was evenly split between males (51.6%) and females (48.4%), the majority was of non-latino/hispanic ethnicity (82.6%), and there was a greater percentage of black patients (41.3%) than white (37%)

or other (21.7%). Medicaid was the predominant type of medical insurance for patients diagnosed with MIH (80.4%), with self-pay (8.7%) and commercial insurance (10.9%) being less common. Participants in the control group had similar demographic patterns.

	MIH			
	No		Yes	
	N	%	N	%
Total	184	100.0%	92	100.0%
Age in months				
Mean	120.78		120.78	
Standard Deviation	34		34	
Min, Max	70, 209		70, 209	
Gender				
Female	89	48.4%	51	55.4%
Male	95	51.6%	41	44.6%
Language				
English	108	58.7%	58	63.0%
Non-English	76	41.3%	34	37.0%
Race				
Black	83	45.1%	38	41.3%
Other	55	29.9%	20	21.7%
White	46	25.0%	34	37.0%
Ethnicity				
Latino/Hispanic	42	22.8%	16	17.4%
Not Latino/Hispanic	142	77.2%	76	82.6%
Medical Insurance				
Commercial	22	12.0%	10	10.9%
Medicaid	151	82.1%	74	80.4%
Self-Pay	11	6.0%	8	8.7%

Table 2: Descriptive Statistics - Demographics

3.3 Environmental Exposures

The study cohort was analyzed using logistic regression for associations between demographic variables and the presence of MIH. There were no significant differences between MIH incidence and gender, race, language, ethnicity, or insurance type. The study cohort was also analyzed using logistic regression for etiological associations between MIH and early environmental events (pre-, peri-, and postnatal), early childhood illness, systemic disease, vaccination, or medication use. Select variables of interest (maternal alcohol, drug/substance, and tobacco use, hypoparathyroidism, hypocalcemia, repaired cleft lip/palate, adenoiditis, fever, and varicella) were not included in this model due to the small number of positive values. The

logistic regression model showed patients who received the DTaP vaccine were less likely to have MIH than patients who did not receive the DTaP vaccine (Odds ratio = 0.3, P-value = 0.01). Variables that were not significant at the 0.05 level, but below the P-value of 0.1, include tonsillitis, cesarean section delivery, and hospitalization **(Table 3)**.

Variable	Odds Ratio	95% Confidence Interval		P-value
Asthma	0.5	0.2	1.2	0.13
Acetominophen	0.9	0.4	1.9	0.77
Antibiotic	0.9	0.4	2.1	0.78
Autism Spectrum Disorder	0.3	0.1	1.6	0.17
DTaP Vaccine	0.3	0.2	0.8	0.01
Developmental Delay	3.8	0.6	24.4	0.16
Epilepsy	0.5	0.0	5.9	0.60
Hospitalization	0.5	0.2	1.1	0.09
Labor and Delivery (C-Section)	0.3	0.1	1.1	0.06
Low Birthweight	0.5	0.1	3.2	0.46
NSAID	1.0	0.4	2.2	0.95
Otitis Media	1.3	0.6	2.9	0.54
Passive Smoke Exposure	0.7	0.3	1.6	0.36
Premature Birth	1.8	0.4	9.2	0.48
Respiratory Infection	0.5	0.2	1.2	0.12
Tonsillitis	2.9	0.9	9.1	0.07

Table 3: Associations between Early Life Events and MIH - Logistic Regression

3.4 MIH Severity

This study assessed potential etiological associations in comparing both mild and severe MIH with a control group, as well as etiological associations between mild and severe MIH **(Table 4)**. Logistic regression was used to assess these relationships. When analyzing exposures between patients with mild MIH vs. severe MIH, patients who had tonsillitis were less likely to have severe MIH than those who did not have tonsillitis (Odds Ratio=0.1, P-value=0.01). When comparing mild MIH to the control group, those who had tonsillitis were more likely to have mild MIH than patients who did not have tonsillitis (Odds Ratio=8.8, P-value=0.001). Compared to the control group, female gender was associated with severe MIH compared to males (Odds

Ratio=2.2, P-value=0.04). In addition, patients who had DTaP vaccine were less likely to have severe MIH than patients who did not have DTaP vaccine (Odds Ratio=0.2, P-value=0.0003). Statistical analysis showed near significant associations between otitis media, passive smoke exposure, and asthma for patients with an increased incidence for mild MIH.

Variable	Odds Ratio	95% Confidence Interval		P-value
MIH Mild vs. MIH Severe				
Tonsillitis	0.1	0.0	0.6	0.01
Otitis Media	3.4	0.8	14.3	0.09
MIH Mild vs. Control				
Tonsillitis	8.8	2.5	31.4	0.001
Passive Smoke Expsosure	0.3	0.1	1.0	0.05
Asthma	0.3	0.1	1.1	0.07
MIH Severe vs. Control				
DTaP Vaccine	0.2	0.1	0.4	0.0003
GENDER Female vs Male	2.2	1.0	4.8	0.04

Table 4: Associations Between MIH Severity and Environmental Exposures

3.5 Assessment of Risk of Bias

A single examiner manually analyzed all charts for inclusion. Clinical photographs were reviewed at this time to confirm inclusion eligibility and determine the extent of MIH severity (mild vs. severe). This method of analysis was chosen to eliminate inter-rater reliability bias. In order to rule out intra-rater reliability bias, the primary examiner randomly selected ten charts following the initial chart review to assess for error in inclusion or severity documentation. There were no changes in severity or participation during the second review.

Chapter 4: Discussion

4.1 Evaluation of Results

These results support previous findings that MIH is a multifactorial, multidimensional diagnosis involving a combination of genetic, environmental, and socioeconomic variables leading to the etiology (1,5,9). Descriptive statistics demonstrated a diverse study population for both categories: those with MIH and their age-matched counterparts without MIH. Consistent with previous studies' findings (6), there was no association between an increased incidence of MIH and age, race, ethnicity, or socioeconomic status.

During the assessment of etiological associations, several environmental exposures were excluded from the logistic regression model due to insufficient documentation in patient health records. Variables that were removed from further evaluation included maternal alcohol, drug/substance, and tobacco use, hypoparathyroidism, hypocalcemia, repaired cleft lip/palate, adenoiditis, fever, and varicella. This was likely the result of a short study timeline,relative rarity of positive findings, and a relatively small sample size.

Interestingly, the DTaP vaccine was the only exposure significantly negatively associated with MIH. These results suggest that the DTaP vaccine may serve as a protective factor against the development of MIH. Statistical analysis showed a near significant negative association of MIH with cesarean section delivery, as well as an increased incidence of MIH with tonsillitis and hospitalization before the age of four. Variables that were previously noted in literature to contribute to MIH such as antibiotic use, fever during the first three years of life, delivery complications, and respiratory diseases (9,12) were not significantly associated with MIH in our study.

This study also assessed potential etiological associations between severities of MIH, mild and severe, as well as both severities and the control group without MIH. Interestingly, the number of patients diagnosed with severe MIH (52%) was higher than those diagnosed with mild MIH (48%). Severe MIH is more obvious to the provider and discrete defects of the enamel such as that of mild MIH may be often missed during routine intraoral examinations.

Tonsillitis appeared to have a negative association with severe MIH compared to mild MIH, but a positive association with mild MIH compared to the control group. These results suggest that tonsillitis before the age of four years old may be a variable of interest for the development of mild MIH.

When comparing patients with severe MIH and the control group, those who had the DTaP vaccine were less likely to have severe MIH than patients who did not have DTaP vaccine. This reinforces the previous suggestion that the DTaP vaccine may serve as a protective factor against the development of MIH. In addition, female gender was associated with a greater prevalence of severe MIH as compared to males. This finding does not align with previous results of meta-analyses (6), and may be attributed to small sample size. Statistical analysis showed near significant associations between otitis media, passive smoke exposure, and asthma for patients with an increased incidence for mild MIH.

4.2 Study Strengths:

This study had many strengths including patient selection, methodology, and data analysis. This is one of the very few prospective studies analyzing MIH etiology with an integrated dental and medical electronic health record. Prospective studies starting around the time of birth to time of eruption of the first permanent molar are superior to retrospective studies to clarify mechanisms behind the defects (1,7). A notable strength was the diverse study population, as it represented

children ages six to 17, with a range of ethnicities, races, and socioeconomic strata, which positively contributed to the external validity of the study.

4.3 Study Limitations:

This study also had notable limitations. As mentioned in literature, maternal data is limited within medical and dental charts (7). Although birth history was documented, the records lacked medical data during pregnancy including tobacco, drug/substance, and alcohol use. It was difficult to quantify qualitative measures, including but not limited to "maternal pregnancy complications," in the initial data query without an identified code to extract this information from the electronic health record. Recent studies have mentioned a major limitation in the MIH literature is the lack of standardized outcome measurements, compromising the validity of a clear conclusion (7). Additionally, while the sample size was adequate to complete this study, a larger population would have increased the number of patients with rare medical conditions (hypoparathyroidism, hypocalcemia, cleft lip/palate repair, etc.), which would have strengthened their inclusion in the regression model. This study relied heavily on individual provider documentation, and a large number of patients were excluded due to lack of clinical photographs taken during routine intraoral examinations. Lastly, the presence of a second examiner would have eliminated the internal bias that is created from having a single data reviewer.

4.4 Future Study Recommendations

This was a pilot study to analyze the etiologies of patients with Molar Incisor Hypomineralization. Future studies can extend the study timeline to achieve a larger sample size. Providers should be recalibrated on taking photographs at regular intervals. A second examiner would eliminate the potential for intra-rater reliability bias. Number of affected molars could also

be studied. Given the multifactorial nature of MIH, genetic components are of interest; laboratory studies in conjunction with epidemiologic investigations should be considered.

Chapter 5: Conclusion

Molar Incisor Hypomineralization remains a multi-dimensional, multi-factorial diagnosis with several potential etiological associations. DTaP Vaccine status is a variable of interest for future MIH studies. Prospective studies with increased sample size and more complete documentation, including maternal data, are needed to further evaluate these etiological associations.

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