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Review Article

**A SYSTEMETIC REVIEW TO DETERMINE THE FACTORS
RESPONSIBLE FOR DEFECTS IN ENAMEL
DEVELOPMENT**Dr Usama Saboor¹, Dr Jamaludin², Dr Wajeeha Ejaz³¹Fatima Jinnah Dental College, Karachi²Bolan Medical College and University, Quetta³DHQ Hospital, Chakwal**Article Received:** November 2019 **Accepted:** December 2019 **Published:** January 2020**Abstract:**

Introduction: Dental enamel is an uncommon tissue in body .Once it is formed, it is not remodeled, unlike other hard tissues such as bone. Because of its non- remodeling nature, alterations of enamel during its formation permanent damage of the enamel is Molar Incisor Hypo-mineralization (MIH)

Methods and results: it can be said that the prevalence of MIH appears to be increasing, and managing affected children is a general problem for pediatric dentists. The etiology is unclear and may be multifactorial, in fact the children born preterm and in their first 3 years with poor general health or systemic conditions may develop MIH. The early identification of such children may permit monitoring of their PFMs so that remineralization and preventive measures can be considered as soon as affected surfaces are visible in oral cavity. In order to provide the complex care, it must address the child's behavior and anxiety, seeking to provide durable and pain-free restorations. It is recommended that it is necessary to consider further research to clarify etiological factors and improve the durability of restorations in affected teeth

Key words: MIH, Enamel, PFM, Hypo-mineralization.

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INTRODUCTION:

Amelogenesis is regulated by ameloblasts and a multifaceted process that requires secretion of certain matrix proteins like amelogenins, amelins, enamelin and tuftelins and of the prior formation of dentine [1,3]. Dental enamel formation occurs in various phases in the primary as well as in the permanent dentition. According to few studies there are two steps [1,2] i.e. the secretory phase [or matrix formation] and the maturation phase while other authors add an intermediate or transitional phase 4 . According to Lacruz amelogenesis can be classified as pre-secretory, secretory, and maturation stages [3]. Genetic and environmental factors have marked influence on these processes; consequently, may result in developmental enamel defects (DED) from any event disturbing these phases. Metabolic or systemic alterations during the formation of dental crown, reflects a permanent impression of systemic disturbances, such as prolonged periods of high fever, nutritional deficiencies, congenital factors, infections, and certain medications can affect enamel-forming cells. A number of known conditions such as diseases, metabolic anomalies, and environmental factors can modify normal enamel development [5,8] alteration resulting from varied turmoil during the process of amelogenesis considered as Developmental enamel defects. DED can be further classified according to their manifestation such as demarcated opacities, diffuse opacities, and hypoplasia 6 primary and permanent dentitions both may be affected, and be associated even to single long -lasting disturbances or isolated events 9 . While according to some authors there are linking events in the deciduous teeth consequences observed in the permanent set of dentition [10,13] . Dental enamel is dissimilar to other hard tissues such as bone in the fact that once formed it is not amend¹⁴. Knowing its non-amending nature, variations of enamel formation is permanently recorded on the tooth surface, the alterations induced in the enamel formation, can give evidences as to the timing and nature of these events¹⁴. Thus many adverse biological events may be reflected as Enamel defects and thus may be considered as a marker of unfavorable measures occurring during the time of its development [14].

EPIDEMIOLOGY:

The literature of the last fifteen year and epidemiologic data is very limited and turned mostly to studies of prevalence. Studies available on the frequency of hypoplasia of the dental enamel in the present-day populations demonstrate the link between the socio-economical conditions and the prevalence of this defect¹⁵. Data from the developed countries reflects the incidence of this

condition for an average of 10%, while in the developing countries the same incidence is markedly higher than the 50% ¹⁵. Data from studies undertaken between the year 1987 and the 2001 are of difficult interpretation because they recorded as secondary result only and do not have objective as the study of prevalence. According to that data they claim that it varies within an ample period of time, included between the 2.8 and 2.5%, up to assumption of a more reliable and constant value that is around the 15%, instantly after such time term [16,28] on the contrary the reflection of more recent epidemiological studies seem to present that the MIH prevalence is increasing day by day ¹⁹. According to the data presented in the study on 3518 Greek children, aged between 5.5 and 12 years, results that: the 10.2% of them (58.6 female and 41.4 male) present Molar Incisor hypo-mineralization (MIH), while the total number of teeth affected almost equal to 1286, of which 776 molars and 510 incisors In the 28.4% of the children influenced by MIH are interested only molars while in the 71.6% incisors and molars both. While the different type of association of the affected teeth noticed that resulted as: 4 molars 2 incisors (23.5%), 4 molars 4 incisors (16.8%), only 4 molars (15.1%), only 2 molars (9.7%) with a main involvement of the maxillary elements in contrast to the lower jaw. Such study also demonstrates that some pathologic condition in progressive in relation to the age because the under observed dental tissue are affected by a post eruptive repartition of the enamel, and determine that the gravity of the MIH increases in a way proportional to the chronologic age ^{19,30}With respect to the gender difference the major part of the studies undertaken between the 2001 and the 2007 demonstrate that it does not exist any difference of distribution among the two sexes ^{18,21-25}. On the contrary, recently some Authors report a major evidence charged to female sex, but with no demonstration of causal relationship ²⁷. There are a number of studies undertaken to establish the average value, per child, of tooth affected by MIH presents that it varies from 5 to 5.7 elements per individual; further more they highlighted that the damages involving the first permanent maxillary molars are the more serious as well as the more frequent ^{18,20,21,23-27,2}.

CLINICAL FEATURES:

By definition MIH is a hypo mineralized defect of the first permanent molars, frequently correlated with affected incisors ³⁰. It is observed that the number of affected first permanent molars is variable per patient from one to four and expression of the defects may vary from molar to molar ³⁰. Intact opacities

Table 3: Clinically differentiation between MIH, Amelogenesis Imperfecta and Fluorosis.

Conditions	Findings
Amelogenesis Imperfecta	Involves all the teeth, family history is present, teeth may appear taurodont on radiograph
Fluorosis	Diffuse opacities which are caries resistant. Number of teeth involved depends on the time of exposure.
Molar Incisor Hypo mineralization	Involves PFM and incisors, well demarcated opacities will be present which will be caries prone. Only severe case may resemble AI. No appearance of taurodont on radiograph.

can be found on one molar within one patient, while the other molar may have large parts of the enamel break down soon after eruption [30]. When a severe defect is found within a subject, it is likely that the contralateral tooth is also affected [30]. In connection to molars opacities may be found in the upper and sometimes the lower and upper incisors, (Figure 1). The possibility of defects to the maxillary incisors appears to increase when more first permanent molars have been affected [30]. The defects of incisors are usually without loss of enamel substance. Clinically, the hypo mineralized enamel appears to be soft, porous and look like discolored chalk or Old Dutch cheese. With respect to color the enamel defects can diverge from white to yellow or brownish and it always demonstrate a sharp demarcation between the affected and sound enamel [31] (Figure 2). The hypomineralized weak and porous, brittle enamel can easily chip off under the masticatory forces. Sometimes, post eruptive enamel breakdown can occur so rapidly after eruption that it seems as if the enamel was not formed initially [31]. It appears as hypo plastic enamel after occurrence of the post-eruptive enamel breakdown. Clinically hypoplasia presents with the smooth borders to the normal enamel, whilst in post eruptive period. Enamel breakdown occurs and the borders of the normal enamel appear irregular [31]. MIH can sometimes be confusing with fluorosis or amelogenesis imperfect [31]. In fluorosis as its opacities are diffuse opacities that can be well differentiated from are demarcated opacities of MIH (fluorosis is caries resistant and MIH is caries prone). Choosing between Amelogenesis Imperfecta (AI) and MIH as a diagnosis seems a matter of definition: it should be stressed that, only in very severe MIH cases, the molars are equally affected and mimic the appearance of AI [32]. Mostly in MIH, the appearance of the defects will be more asymmetrical in the molars as well as in the incisors. In AI, the molars may also appear taurodont on radiograph and there is often a history of family onset [31].

ETIOLOGY:

The uneven appearance of MIH molars within individuals' depicts that a systemic disorder at a very specific stage affects the development of ameloblasts. According to the current data the researchers hypothesize that, in the case of MIH, the ameloblasts are affected in the early maturation stage, or maybe even earlier at the late secretory phase. In the recent studies, various causes for MIH molars, such as environmental conditions, respiratory tract problems, perinatal complications and dioxins have been suggested [17,30,32,33]. Other factors responsible for MIH available in the literature are oxygen starvation of the child combined with a low birth weight, calcium and phosphate metabolic disorders and frequent childhood diseases [34-36]. Vaccines given during early childhood have also been suggested as a possible cause but no data are available to validate this. The use of antibiotics has also been implicated, but antibiotic use is in most cases related to occurrence of diseases, so it is difficult to distinguish whether the association with MIH is caused by the antibiotic or by the illness itself. There are contradictions in the results of the different studies about it. A number of studies relate the problems during pregnancy and birth with the MIH, while in other studies show no differences concerning the health of mother and child during pregnancy and birth of the children [33,36]. The latter study indicates a more child related cause originating after birth. The influence of prolonged breast-feeding could not be demonstrated in all studies [17,36-38]. It is likely that several unknown contributing factors are involved resulting in a number of possible causes [37, 38]. A study conducted in Greece of 151 MIH children resulted that 78% had experienced medical problems: (1) prenatally (19%); (2) perinatal (44%); and (3) neonatal (22%) [41]. Only 15% of the children did not appear to have a putative etiological factor in their history [39]. Studies available do not suggest any causal relationships because it cannot be assigned definitively from studies relying on parental recall of medical and dental events in their child's first 3 years [40, 41]. It becomes more difficult to determine the etiological factor when it is

associated with a number of medical problems in this period. Although a number of causative factors may contribute to MIH but the threshold level needed to cause enamel defects and at which sensitive stages of amelogenesis is unknown⁴². It is assumed that systemic illnesses may not produce a developmental defect of enamel when experienced singly, and two or more concurrent conditions may act synergistically to produce a defect [42]. It is also in accordance to the study of 53 Swedish children with 22q11 microdeletion syndrome⁴³. Phenotypically, this multiple anomaly has a characteristic facies, and may include congenital heart defects, velopharyngeal insufficiency which may include cleft palate, immune deficiencies, and difficulty in feeding, hypocalcemia, learning disabilities, behavioral problems, and skeletal, neurologic, and gastrointestinal abnormalities [43]. Of 47 affected children, 3 (6%) had EH in the permanent dentition and 16 (34%) had hypo mineralized permanent teeth. Computerized inductive analyses showed that the EH of permanent and primary teeth correlated with prematurity and heart defects (30%) and enamel hypo mineralization correlated with frequent preschool age infections and heart defects (43%)⁴³. Infectious conditions common in the first 3 years, such as upper respiratory diseases, asthma, otitis media, tonsillitis, chicken pox, measles, and rubella, appears to be associated with MIH. [4, 45]. It is also reflected in the retrospective study of 21 Dutch MIH children, 67% had suffered from bronchitis, asthmatic bronchitis, pneumonia, and upper respiratory tract infections⁸. The usage of antibiotic has also been implicated. Due to the harmony of disease and antibiotic therapy, though it is difficult to ascertain whether the MIH was associated with the disease or the antibiotic [45]. Literature shows that children with poor general health and systemic conditions are more likely to have developmental defects of enamel [46, 47]. As the mineralization of Permanent First Molars (PFM) commences soon after birth, a persistent systemic derangement postnatally may affect enamel mineralization [50]. Preterm birth can be associated with a number of systemic conditions such as respiratory difficulties, hyperbilirubinemia, metabolic disturbances including hypocalcemia and hypoglycemia, hematological disorders, patent ductus arteriosus, and intracranial hemorrhage [48]. A study of 32 Finnish children 9 to 11 years old found enamel defects in 36% of children born full term and 84% of children born preterm⁴⁹. It is suggested that the severity of enamel defects increased with decreasing gestational age and lower birth weight [50]. A number of clinical and laboratory studies reflects the associations between the presence of polychlorinated dibenzo-p-dioxins (PCDDs) in breast milk and enamel hypo mineralization [51,52]. it belongs to a class of environmental pollutants known as polyhalogenated

aromatic hydrocarbons⁵¹ that results in long term persistent exposure in humans and accumulation of PCDDs in tissue lipids and in the food chain [53]. Other clinical studies have not found any associations between dioxin compounds in breast milk and were born preterm or who were exposed to certain environmental contaminants may be at risk for MIH.

Tooth discoloration related to drug: There are a number of known drugs responsible for producing extrinsic or intrinsic tooth discoloration.

(a) Extrinsic Tooth Discoloration related to Drug: This type of discoloration appear after the tooth has erupted in the oral cavity, in this case drug is responsible for subsequent cause of superficial discoloration, tooth-bushing or professional cleaning are the methods for its elimination. According to number of authors there are a number of drugs that are well known to be causing extrinsic discoloration include chlorhexidine [54-56], oral iron salts in liquid form essential oils [57] and Coamoxiclav [58]. Netherlands Pharmacovigilance Foundation (LAREB) published abundant data from January, 1991, until June, 1995, of oral use of liquid medication causing yellow to brown tooth discoloration out of which 84% involved antibiotics, particularly amoxicillin⁵⁹. Another source of data depicts the tooth discoloration problem accredited to the use of drugs, frequently to the use of amoxicillin and doxycycline or minocycline. Antimicrobial agents mostly cause the Pseudo-discolorations; mechanism may involve the chromogenic precipitates accumulation in the pellicle, or by chromogenic micro-organisms overgrowth⁵⁹. With the increasing frequency of methicillin-resistant *Staphylococcus aureus* in immunocompromised hosts, clinicians are increasingly prescribing the oral antimicrobial linezolid, an oxazolidinone. A case of an immunocompromised 11-year-old girl was reported with cellulitis and the development of superficial discoloration of her lower anterior teeth after receiving linezolid for 28 days [60].

(b) Intrinsic Tooth Discoloration related to Drug: It is Permanent type of tooth discoloration occurs when the drug interferes with odontogenesis. A number of causative agents are known but we will discuss only Fluorides and Tetracycline.

(i) Fluorides: Inorganic fluorides plays a pivotal role in reducing the extent and severity of dental caries in children and adults⁵⁹. It also has some unfavorable effects in humans that depends upon the level and source of exposure [59]. There are many sources of getting fluoride in routine like water, toothpaste, prescribed drops, and tablets, upon which the discoloration depends specially at the time of tooth development stages like formation and maturation phase. Over exposure to fluoride ion causes Dental fluorosis, which is the most common adverse effect and may end up to the permanent hypo mineralization of enamel. This type of hypo

mineralization can be recognized clinically in its mildest form as small, barely visible, white flecks found mostly on cusp tips and on facial surfaces of the permanent teeth⁶¹. While the severity ranges from white opaque areas to darkly stained and pitted enamel, ⁶¹ that is visible on most surfaces of permanent teeth. Exposure to fluoride in early maturation stage of tooth development is considered to be critical for fluorosis to evident [61]. Dental fluorosis is a dose-dependent condition, according to Dean in 1942 that shows a direct relationship. The higher the level of exposure during tooth development, may lead to the more severe fluorosis⁶². The normal range of fluoride to be taken in tooth development period i.e. from approximately birth to 8 years of age, is in the range of 0.03 to 0.1 mg/kg body weight per day [62].

(ii) Tetracycline It was hypothesized by Olsen and Riley hypothesized that tetracycline may cause permanent tooth discoloration in 1960's⁶³. Subsequent to this hypothesis many clinical and laboratory studies exhibited the association that tetracycline make an irreversible bond to calcified tooth structures, if it is exposed during the calcification stage of hard tissue⁶³. Today it is a proven fact that Tetracycline are result in the discoloration of hard tissue of the body when prescribed during its development. Discoloration of deciduous teeth may occur in result to exposure to tetracycline during the second or third trimester of pregnancy. During development, the teeth may become bright yellow while the stains will later turn to grey or brown over a period of time [62].

PREVENTIVE MANAGEMENT:

Children with MIH repeatedly experience pain, sensitivity and aesthetic concerns when their incisors are affected. A management approach based on 6-steps is proposed (Table 2). It is suggested that MIH risk children should be diagnosed prior to eruption of PFM, this diagnosis should be based upon a relevant history of assumed etiological factors in the first 3 years and from careful study under magnification of the unerupted molar crowns on any available radiographs. Knowing the fact that during PFM eruption, the hypo mineralized surface is very susceptible to caries and erosion. The child's diet should be assessed and appropriate recommendations made for reduction of cariogenicity and erosivity of the diet. Meticulous oral hygiene should be maintain. Desensitizing toothpaste can be recommended along with Remineralization therapy should commence as soon as the defective surface is accessible, in order to produce a hyper mineralized surface layer and to desensitize the tooth [41,65]. Process of remineralization and desensitization may be accomplished with casein phosphor-peptide-amorphous calcium phosphate (CPP-ACP) oral care products. The CPP-ACP can interact with fluoride

ions, producing an amorphous calcium phosphate stabilized by CPP at the tooth surface and providing soluble calcium, fluoride, and phosphate ions to promote remineralization with Fluor apatite that is more acid resistant [66]. Topical fluoride available as varnishes/ gels, delivered as concentrated, can re mineralize enamel, enhance resistance and reduce sensitivity to demineralization by providing a reservoir of fluoride ions for re deposition as Fluor apatite during remineralization [67]. Regular oral hygiene strategies can be instituted as remineralization and desensitization of the affected molars occurs. Glass ionomer cement sealants can provide caries protection and reduce surface permeability for partially erupted PFMs where moisture control is suboptimal. However, such sealants may need rebuilding later because of poor retention, reconstruction with a resin-based sealant when optimal moisture control is possible is recommended ^{68, 69}. If preventive care is not provided, hypo mineralized PFMs are at risk of PEB in the acidic and masticatory challenges of the oral cavity. PEB will lead to increase the porosity of subsurface enamel or dentin and will result in teeth to become sensitive to cold air, warm water, and tooth brushing ³⁷. Moreover, deprived oral hygiene will lead to plaque retention and promotes rapid caries development [70].

CONCLUSION:

In conclusion it can be said that the prevalence of MIH appears to be increasing, and managing affected children is a general problem for pediatric dentists. The etiology is unclear and may be multifactorial, in fact the children born preterm and in their first 3 years with poor general health or systemic conditions may develop MIH. The early identification of such children may permit monitoring of their PFMs so that remineralization and preventive measures can be considered as soon as affected surfaces are visible in oral cavity. In order to provide the complex care, it must address the child's behavior and anxiety, seeking to provide durable and pain-free restorations. It is recommended that it is necessary to consider further research to clarify etiological factors and improve the durability of restorations in affected teeth.

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