Enamel hypoplasia and enamel pre-eruptive hypomineralisation in the secondary dentition: a narrative review of literature

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Abstract

Aim The aim of the study was a narrative review of scientific literature about enamel defects such dental hypoplasia and pre-eruptive hypomineralisation. A preview detailed description about enamel formation during its secretion and maturation stages was conducted.

Methods Databases such PubMed, Embase, Scopus, ResearchGate and Cochrane Database of Systematic Reviews were used for the papers research used for that narrative review.

Results In that narrative review of scientific literature are collected detailed information about the biological process occurs during secondary enamel formation and that make possible a distinction between quantitative enamel defect such dental hypoplasia and qualitative defects such pre-eruptive enamel hypomineralisation disease. The most accredited aetiology factors and pathogenesis process are taken into account.

Conclusions Enamel pre-eruptive defects are not similar each to the others and have a different biological formation mechanism during the secretion or maturation stage of enamel that occurs during the first months of life. These defects are different not only in the formation process but also in clinical appearance, clinical treatment and prognosis. Not fully clear are the aetiology factors and pathogenesis mechanism at the base of pre-eruptive enamel defects. Some validated hypothesis has a scientific and rationale support to explain the enamel pre-eruptive defect.

KEYWORDS Enamel secretion stage, enamel maturation stage, enamel hypoplasia, enamel pre-eruptive hypomineralisation, dental fluorosis.

Introduction

During dentist children's visits after secondary teeth eruption, it is possible to find some enamel defects that are different each from the other for genesis, clinical aspect and evolution during life. These defects are classified as pre-eruptive because they develop during enamel formation in the early stage of children's life and are substantially different from post-eruptive defects, such as enamel demineralization process from aciduric bacteria of mature dental biofilm [Patel et al., 2019; García-Godoy and Hicks, 2008]. Both of these enamel defects are related to alteration of enamel protein matrix during the secretion or maturation stage and they can be a quantitative or qualitative defect. Enamel hypoplasia is an enamel quantitative defect related to a localized lack of enamel protein matrix secretion into the enamel organ during amelogenesis. Enamel pre-eruptive hypomineralisation is an enamel qualitative defect where a normal enamel matrix secretion follows a localised, or more extended, lack of mineralisation of the matrix during amelogenesis. Enamel hypoplasia and pre-eruptive demineralisation are two clinical conditions substantially different not only for pathogenesis but also for the clinical aspect and prognosis [Jacobsen et al., 2014]. Localized enamel hypoplasia does not affect the health of the tooth but often is just an aesthetic problem if it appears in anterior teeth. If enamel hypoplasia is diffused and the defect is particularly deep, together they could be a locus of plaque accumulation and a risk factor for the development of carious lesions due to the brushing difficulties in the bottom of the defect. Pre-eruptive hypomineralisation is a more articulated disease because takes into account more defects with the same pathogenesis but different evolution and prognosis of the affected tooth and it depends on the clinical aspect and severity of the defect. Between pre-eruptive defects is possible to find different diseases such as Molar-Incisor-Hypomineralisation MIH, Molar-Hypomineralisation MH and dental fluorosis.

Materials and methods

The study design and protocol used a strategy to search the papers for the narrative review of scientific literature. Databases such as PubMed, Embase, Scopus, ResearchGate and Cochrane Database of Systematic Reviews were used for papers research. The following keywords were employed in the search strategy to find related articles: enamel defects, enamel formation, enamel hypoplasia, enamel pre-eruptive hypomineralisation, Molar-Incisor-Hypomineralisation, and dental fluorosis. Eligibility criteria for studies inclusion and analysis take into account only papers written in English language.

Amelogenesis of secondary teeth

Amelogenesis is the biological and chemical process that leads to dental enamel formation and for secondary dentition it starts a few months after children's birth [Sabel et al., 2009]. Enamel development involves two functional stages such enamel matrix secretory and its maturation, with a brief transition between the two stages. Dental enamel is an epithelium tissue (ectodermal embryological origin) that started by dental lamina formation inward into a mesenchyme substrate. The dental epithelium lamina rapidly penetrates the underlying mesenchyme followed by the placode, bud, cap and bell stages at the end of the process. At the bell stage, the dental crown tissues and the shell of dental enamel are well represented. The dental enamel cells are already differentiated from mesenchyme to epithelium cells into the enamel organ [Chaiet al., 2000]. To understand amelogenesis Is important to know the concept of the enamel organ, the constituent cells, their function and disposition and the vascular network that supplies nutrients to the development of the enamel organ. Amelogenesis involves the presence of different epithelium-derived cell types that change in form, presence and function between the enamel matrix secretory and maturation stage [Hu et al., 2007]. The innermost layer of the enamel organ is a single layer of cells that differentiate into ameloblasts that appear

vertically orientated toward the periphery of the dental crown and with long Tomes' process projected toward the next and inner enamel dentin junction "DEJ". The outermost layer is also a single layer of cells called outer enamel epithelium and the innermost ameloblasts layer and the outer epithelium layer converge at the cervical region of the enamel organ. Between the inner and outer enamel organ areas, other intermediate layers of epithelial stem cells are represented and they have a certain role during the secretory and maturation stage of enamel until the enamel shell is fully formed. Is possible to recognise the intermediate layers of the enamel organ, during secretory stage for example, a group of thick cells called the intermedium layer and a larger grouping of star-shaped cells called stellate reticulum. The vascular network for the development of enamel organ is associated with the outer enamel epithelium layer [Harada et al., 1999; Juuri et al., 2012].

Enamel matrix secretion

The innermost layer of an enamel organ is formed by a polarised and elongated secretory ameloblast able to synthesize and secrete some structural enamel matrix proteins (EMPs) and in particularly amelogenin, ameloblastin and enamelin [Smith, 1998]. The elongated Tomes' processes are most important during the secretory stage because the distal part of Tomes' process penetrates the bottom of the enamel matrix secreted and released here, for exocytosis, other secretory vesicles. The enamel matrix is a very soft tissue (gel-like) that contains similar amounts of enamel matrix proteins EMPs, minerals and water in near-neutral pH conditions [Lacruz et al., 2010]. The precursors of the enamel crystals (nucleation) start already during the early stage of matrix secretion and are thin crystals of hydroxyapatite (Hap-like) that elongate perpendicular to the dentin-enamel junction "DEJ" toward the outermost layer of the enamel organ. The nucleation of hydroxyapatite crystals and their growth are guided under the influence and regulation of EMPs present in the enamel matrix secreted. The growth direction of hydroxyapatite crystals will follow the movement of the ameloblast away from dentin at the end of the enamel matrix secretion stage [Fincham et al., 1995; Nanci, 2008]. Some recent data suggest that the nucleation and the initial growth of hydroxyapatite crystals do not start from the innermost enamel matrix secreted by ameloblast cells but into the near dentine in a region that will be represented by enamel-dentin junction "DEJ". Hydroxyapatite crystals then elongated away from dentine follow the long axis of ameloblast toward the outermost layer of the enamel organ [Smith et al., 2016]. That hypothesis is fascinating because might explain the ultrastructure of dentin-enamel junction "DEJ" and its function to dissipate the load carried out to the stiff enamel during bite function in order to prevent tooth fracture. During the secretory stage, the ameloblast are tight opposed each to other and are connected by intercellular tight junction on the lateral membrane at both basal and apical (Tomes's process) zone. Tits tight junction between the secretory ameloblast forms a semipermeable barrier for intercellular movement and diffusion of mineral ions from the outermost blood network to the secreted enamel matrix [Hubbard, 2000]. Almost the entire thickness and volume of enamel is laid down during the enamel matrix secretory stage.

Enamel matrix maturation

The enamel matrix maturation is preceded by a brief transition stage. During the transition stage is possible to assist at some important ameloblast changes that over their secretory activity, become shorter and lose their secretory Tomes' process and a great percentage of ameloblasts die for apoptosis as a result of calcium overload [Hubbard, 2000]. In the transition stage, not only cell modification occurs but also important gene expression profiles and in particular a gene downregulation coding for enamel matrix proteins EMPs such as amelogenin, ameloblastin and enamelin. On the other front, the genes involved in ions transport, proteolysis and pH homeostasis are upregulated [Hu et al., 2012; Lacruz et al., 2012]. During enamel maturation the most activity of the shorter ameloblast including ions transporter, acid-base balance, enamel matrix proteins EMP removal or endocytosis and at the end ameloblast apoptosis [Lacruz et al., 2010; Lacruz et al., 2013]. Hydroxyapatite crystal formation starts in the secretory stage and is completed during the maturation stage where the crystals expand in width and thickness and follow a direction perpendicular from the dental enamel junction "DEJ" toward the periphery of the dental crown. At the end of the maturation phase, the dental enamel has its characteristic durability and hardness. The short ameloblasts, before their apoptosis, differentiated in two cell variants with specific morphology aspect and function. The first variant of short ameloblast has a greater capacity to transport ions into the enamel organ and degrade the enamel matrix proteins ENP debris. The second variant of a short ameloblast has a less tight junction between the cells and may allow intercellular movements of fluids that are important to contribute to the neutralization of pH in the residual enamel matrix. Both the short ameloblasts present in the maturation stage have, to different degrees, a role in the strict regulation of local pH and bicarbonate ions transport in order to have dominant neutral-alkaline conditions that are most important for the growth of hydroxyapatite crystals. A particular variety of tits short-type ameloblast has, during the maturation stage, an upregulation for carbonic anhydrase-2 an enzyme that is involved in the local production of bicarbonate. In saturated aqueous calcium phosphate solutions with a range of pH from 6.0 to 7.4 is possible to assist in the precipitation of hydroxyapatite according to a quite correct stoichiometric formula. Precipitation of hydroxyapatite results in the release of protons prone to acidifying the solution and that requires active pH regulation by the short ameloblast via bicarbonate ions [Lacruz et al., 2017].

Ultrastructure and chemical composition of mature enamel

The morphology and ultrastructure of dental enamel is unique and different from other mineralised tissues with some distinctive mechanical properties from human bone and dentine. Dental enamel is composed of more than 95% mineral percentage organised in hexagonal hydroxyapatite crystals and is the hardest human tissue without cells presence (apoptosis of ameloblast at the end of maturation stage). These crystals are roughly parallel each to others to form highly organized architectural units called enamel prisms [Cao et al., 2014]. The long axes of the enamel prisms are oriented radially from enamel dentin junction "DEJ" and intercept the occlusal surface perpendicularly. The outer crown layer of enamel (average about 30 microns) is not organized in prisms and is called aprismatic enamel. Between the enamel is present a very little portion of hydrate organic substance (around 3%-4% of weight) like proteins and glycoproteins. In the hydroxyapatite crystals Calcium and Phosphate are far from being stoichiometric correct and often are rich in defects [Dorozhkin and Epple, 2002]. One of the most stoichiometric defects in the hydroxyapatite crystals are usually calcium depletion and to maintain electron neutrality the phosphate groups are replaced by carbonated ions in order to form carbonated apatite. Carbonated apatite has a high chemical solubility and therefore the crystal is much more susceptible to acid dissolution after acid attack from aciduric bacteria of cariogenic biofilm.Carbonated

apatite dissolves at a pH of around 5.0 [LeGeros et al., 1969]. On the other side fluoride is able to fit perfectly into the apatite crystal (to replace the hydroxyl or carbonated group) to form fluorapatite crystals that solubilises at pH around 4.0 and so are more acid resistant [Simmer et al., 2020].

Enamel hypoplasia: clinical aspects, pathogenesis and aetiology related factors

Enamel hypoplasia is defined as a local deficiency in enamel formation during amelogenesis [Masri et al., 2021]. Children presenting enamel hypoplasia had two or more teeth affected and the maxillary incisors were the most frequently affected. Tits pathologic manifestation appears as pits, grooves or lack of enamel surface and generally does not compromise the health and colour of the tooth but just sometimes acquires yellow or brown discolouration due to the deposition of extrinsic pigments [Nikiforuk and Fraser, 1981]. Around and the deep of hypoplasia defect the enamel is represented by sound enamel. The pits and grooves more pronounced are favoring factors to development of carious lesions because in the deep of the defect cariogenic bacteria biofilm can grow, become mature and demineralize the sound enamel of the defect. Enamel hypoplasia is a quantitative defect of mature and permanent enamel and its genesis is related to a lack during the secretion stage of enamel matrix by ameloblast of enamel organ. The pathogenesis of enamel hypoplasia is hypothesized due to a disruption of ameloblast during their secretory activity. Between the etiologic factors related to enamel hypoplasia some systemic factors such as early post-birth renal diseases are most discussed in scientific literature. Ibarra-Santana et al. [2007] in a cross-sectional study and in a population sample of 42 patients ranging in age from 7 and 15 years old describe that none of the patients without renal disease presented enamel hypoplasia. Eight patients (38,09%) with renal disease presented enamel hypoplasia with four of those with defect equal or greater than 2.0 mm. The data reported was statically significant ($p<0.05$). Other studies reported the relationship between post-birth renal disease and enamel hypoplasia [Naylor and Fredericks, 1996; Davidovich et al., 2005; Lucas and Roberts, 2005]. Some clinical correlation was found between post-birth celiac disease and enamel hypoplasia but, on the other hand, other studies do not find a statistically significant correlation between celiac disease and enamel hypoplasia [Rea et al., 1997; Procaccini et al., 2007]. A systematic review suggests that there is an association between prenatal vitamin D levels and the prevalence of enamel defects and tooth mineralization (susceptibility to tooth erosion) [Tapalaga et al., 2023](Table 1).

Enamel pre-eruptive hypomineralisation: clinical aspects, pathogenesis and aetiology related factors

Pre-eruptive enamel demineralization is a condition where less enamel mineral content is present before tooth eruption.That condition is not a localized volume lack of enamel protein matrix EPMs during secretion stage, such as hypoplasia, but a disease related to the maturation stage of enamel. The enamel pre-eruptive condition could be due to an insufficient breakdown of enamel matrix proteins EMPs or an insufficient apport of minerals, such as Calcium and Phosphate, into the enamel organ during its maturation stage. Pre-eruptive enamel hypomineralisation is a qualitative disease of enamel. Enamel maturation stage consists of an increase in the mineral density in the enamel organ and at the same time reabsorption of enamel matrix proteins EMPs by a proteolytic activity of some agents that are involved in the proteins breakdown such kallikrein proteinase-peptidase 4 (KLK4) and some metalloproteinases including numbers 2, 3 and 9 (MMP2, MMP3, MMP9) [Daniele, 2024]. Some enamel hypomineralisation conditions as classified as pre-eruptive disease and between these is possible to cite the Molar-Incisor-Hypomineralisation MIH and the Molar Hypomineralisation MH and the dental fluorosis. The clinical aspect of enamel pre-eruptive hypomineralisation are different for aspects and severity. In the mild condition the disease appears as a white /cream or yellow/brown spot in the sub-superficial layer of enamel but in the severe condition tits colour and aesthetic conditions are accompanied by local enamel breakdown. The local and severe enamel breakdown can get complicated with development of local dentine exposition and dental hypersensitivity or dentine carious lesion disease till extreme tooth crown disintegration [Ghanim et al., 2017]. Scientific literature reports several molecular situations that could be responsible for the qualitative defects in dental enamel such:

ENAMEL HYPOPLASIA	HYPOTHETICAL ETIOLOGICAL FACTORS
	• Renal disease • Celiac disease • Pre-birth vitamin D deficiency

TABLE 1 Systemic post-birth factors and prenatal conditions related to tooth's children dental hypoplasia.

- **Alterations in the production of bicarbonate ions by ameloblasts**

During the maturation stage of enamel matrix there is a release of protons that are neutralized by bicarbonate ions secreted by ameloblasts. As previously cited, a reduced ability of ameloblasts to buffer the enamel organ local pH during maturation stage has been reported as a possible cause of pre-eruptive enamel hypomineralisation defects [Lin et al., 1994].

- **Ionic imbalances altering mineralization processes**

Ameloblasts during maturation stage use different ionic transport systems to include Calcium ions into the enamel organ and obtain mineralization of enamel. A deficit in the inclusion of Calcium ions can produce a lack of enamel mineralization and numerous chemical elements are able to interfering with Calcium transport such Magnesium and Fluoride. An excess of Fluoride can "stress" the ameloblasts activity with alteration about proteinase of enamel matrix proteins EMPs activity. The final outcome of an extracellular excess of the fluoride ions is expected to be a downregulation of the kallikrein proteinase-peptidase 4 (KLK4) during maturation stage of enamel with retention of proteins in the enamel organ and presence of hypomineralised, porous and less hard enamel areas. Retention of enamel matrix proteins EMPs can also interfere with the growth of enamel apatite crystals [Suzuki et al., 2014].

- **Excessive presence of serum albumin in enamel organ**

Although in the pre-eruptive hypomineralisation defects amelogenins have been found as enamel matrix proteins EMPs retained these are not the most represented with a great concentration of serum albumin which can reach a concentration 15 times higher than in healthy dental enamel. Serum albumin is a protein not secreted by ameloblasts during secretion stage (as amelogenin, ameloblastin and enamelin) but, when found, represents an external source into the enamel matrix proteins EMPs. The tight junctions between ameloblast are less permeable to elements that come from vascular network during maturation stage and the serum albumin, with its high dimension, is not

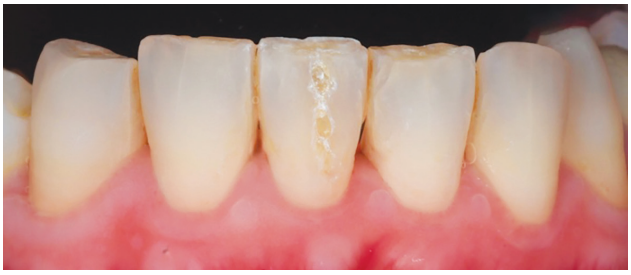

FIG. 1 Enamel hypoplasia on 41.

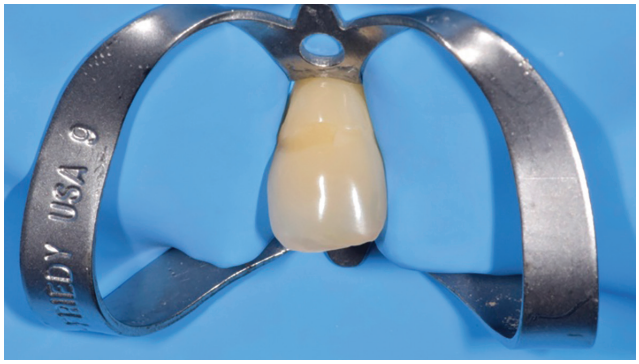

FIG.2 Enamel hypoplasia on 12 before adhesive's restoration for aesthetic request from the patient.

able to overpass the tight junction between ameloblast in physiological conditions. When apatite enamel crystal grows and is no longer coated by amelogenins (proteolysis of amelogenin) other proteins can bind the early stage of apatite crystal and block its growth. Many etiological factors are able to increase the permeability of the tight junctions between ameloblasts during maturation stage of enamel and are responsible for an increased concentration of serum albumin within the enamel organ with the consequences mentioned above. Animal studies suggest that inflammatory mediators are able to influence the function of the tight junction between the cells of retina, kidney and salivary glands and it is possible that a series of local conditions such trauma or inflammation or systemic circumstances can influence a passive increase of serum albumin from the blood network toward enamel organ during maturation stage [Zhang et al., 2016; manton et al., 2016]. Considering that alteration affecting the dental enamel occurs in the peri - or - post natal age, some in vitro studies have found in the pre-eruptive hypomineralisation enamel disease a variable concentration of alpha-fetoprotein which is a fetal isoform of serum albumin. The mechanism of action of alpha-fetoprotein does not differ from that described for serum albumin with its ability to bind the apatite crystals and block its growth during enamel maturation stage. Serum albumin and alpha-fetoprotein appear resistant to the proteolytic action of proteinase such kallikrein -peptidase 4 (KLK4) and that is an adjunctive negative factor affecting the growth of enamel apatite crystal [Williams et al., 2020]. Molar-Incisor-Hypomineralisation MIH is one of the most enamel pre-eruptive defect and its prevalence is variable in the different countries (from 2,4% to 40%) and there is a significant difference in carious lesion prevalence between the group of patients with MIH and the control group with caries index scores (DMFT, DMFS) that increase proportionally to the severity of MIH [Villani et al., 2023]. Molar-Incisor-Hypomineralisation MIH is described in literature with unique and specific clinical aspects but the pathogenesis, the etiological factors responsible for tits pre-eruptive enamel hypomineralisation disease are not yet full identified [Cots et al., 2024; Giuca et al., 2020; Beretta et al., 2020]. As aetiological factors also the clinical approach to Molar-Incisor-Hypomineralisation MIH have not a defined guide lines but different therapy strategy with the only certainty condition that on the pre-eruptive hypomineralised enamel the adhesive's procedures do not work well and cause dislocation of composite resin restoration [Moscati et al., 2024]. The most important goal in children with severe Molar-Incisor-Hypomineralisation MIH is to avoid hypomineralised enamel breakdown until the patient reaches adolescence age and will be possible to have more compliance of the patient, remove the hypomineralised enamel layer and make a definitive restoration [Pardo et al., 2024]. A recent systematic review and meta-analysis [Garot et al., 2022], but also another publication [Bagattoni et al., 2022] has identified a series of possible etiological factors involved in Molar-Incisor Hypomineralisation MIH, attributing to them a specific association ratio (Odds Ratio OR) and classifying as follows:

- Prenatal factors

Diseases affecting the pregnant woman can be responsible for the appearance of MIH with an association ratio (OR) of 1.49% and a narrow confidence interval. No statistically significant association ($p<0.05$) was observed between smoking, drug intake, hypertension and gestational diabetes and the onset of MIH.

- Perinatal factors

Among the perinatal factors and the onset of MIH, a positive and statistically significant association was observed with the phenomena of hypoxia at birth (OR=2.76), cesarean section (OR=1.45) and premature birth (OR=1.45). All the association ratios indicated above have a narrow confidence interval.

- Postnatal factors

Postnatal factors are those most considered and associated with the onset of MIH and among these are considered phenomena of otitis (OR = 1.40), measles (OR = 1.75), urinary tract infections (OR = 1.34), bronchitis (OR = 1.25). All the above-mentioned factors present both an association with MIH conditions and a narrow confidence interval, an element that

PRE-ERUPTIVE ENAMEL Hypomineralisation	HYPOTHETICAL ETIOLOGICAL FACTORS (MIH mainly)
Prenatal factors	• Diseases affecting the pregnant woman
Perinatal factors	• Hypoxia at birth • Cesarean section • Premature birth
Post natal factors	• Otitis • Measles • Urinary tract infections • Bronchitis • Fever episodes • Renal disorders • Asthma • Use of antibiotics in childhood • Fluoride excess intake from 0 to 72 months of age

TABLE 2 Hypothetical etiological factors involved in enamel pre-eruptive hypomineralisation disease (MIH mainly).

strengthens the relationship between the disease and etiological factors. Other postnatal factors taken into consideration are gastric disorders (OR = 1.99), fever episodes (OR = 1.40), renal disorders (OR = 2.70), asthma (OR = 1.55) and use of antibiotics in childhood (OR = 1.21). These etiological factors present a narrow confidence interval even if, compared to the initial ones, they derive from the comparison between clinical studies that are quite heterogeneous among themselves. Excess of fluoride intake between 0-72 months of life is related to the appearance of enamel fluorosis in different degrees and severity [Morris et al., 2022] (Table 2).

Results

The narrative review collected detailed information about the biological process of secondary enamel formation and the final ultrastructure of enamel before tooth eruption. A strictly distinction has made between quantitative defects (hypoplasia) and qualitative defects (pre-eruptive hypomineralisation disease) during enamel formation. A review about aetiology and pathogenesis process of enamel defects highlighted the most accredited factors and theory involved in the process.

Discussion

Tooth's enamel formation is a complex process that to better understand is separated in two phases such secretion of enamel matrix proteins EMPs stage and a next maturation stage where the matrix proteins EMPs are disintegrated and, in the same time, enamel apatite crystal growth. At the end the result is enamel formation that is the hardest and mineralized tissue of the body and without cells for the apoptosis of the ameloblast. During amelogenesis is possible that some defects affected the integrity and mineralization of the enamel and these defects are classified as pre-eruptive because are not dependent from interaction between oral ambient and the mature enamel. Enamel pre-eruptive defects can be a quantitative defect such enamel hypoplasia or qualitative defects due to a little or extended areas of enamel hypomineralisation such Molar-Incisor-Hypomineralisation MIH, Molar-Hypomineralisation MH or dental fluorosis. The aetiology and pathogenis of enamel pre-eruptive defects are not certain but some reliable hypothesis and factor are taken into account and not easy is to collect epidemiological data because they depend from geographic area and the socio-economic status of the children affected [da Silva Júnior et al., 2023; Massoni et al., 2009; Alkhtib et al., 2016]. Dental fluorosis is an enamel hypomineralised pre-eruptive defect that is more certain as etiologic factor and is related to an excess of fluoride intake (toothpaste, drops, drinking water) in the early stage of life from 0 to 72 months that is the interval of secondary enamel formation.

Conclusion

Pre-eruptive defects develop during the first months of life during secondary enamel formation but are substantially different each to others both in diagnosis and clinical treatment. Enamel hypoplasia is a quantitative defect that appear as a local lack of enamel such pits or grooves on the enamel surface with one or more maxillary central incisors involved. Enamel hypoplasia is, in the most of the cases, just an aesthetic defect that can be untreated or treated with a small adhesive's restoration. Enamel pre-eruptive hypomineralisation is a local or more extended lack of mineralization of sub superficial enamel and can result in some colored (white, yellow or brown) spots on tooth enamel surface or, in the most severe situation, become in enamel disintegration with dentine exposure (dentine hypersensivity, higher risk of carious lesion). Clinical treatment of enamel pre-eruptive hypomineralisation is not easy to decide and it depend from severity and position (molar or incisor) of the defect.

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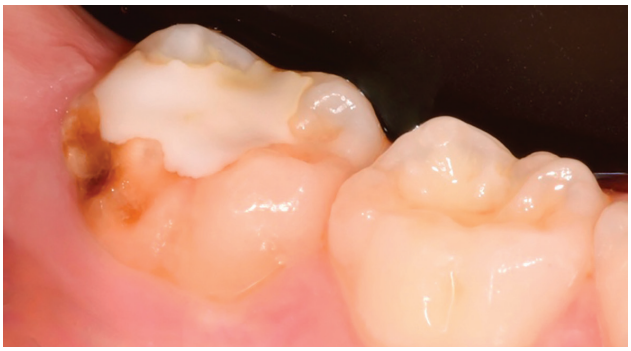

FIG.3 46 Enamel pre-eruptive hypomineralisation defect in Molar-Incisor-Defect MIH disease with enamel breakdown.

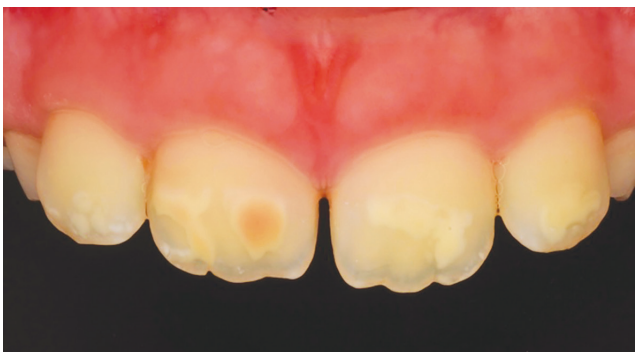

FIG.4 Brown and creamy spots on maxillary central and lateral incisors in a patient MIH affected shoot by cross-polarized image.

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