Drugs related to the etiology of molar incisor hypomineralization

A systematic review

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ABSTRACT

Background. Molar incisor hypomineralization (MIH) is an idiopathic syndrome that has been associated with several etiologic factors. The authors' objective was to systematically review studies in which the investigators had studied how the etiology of MIH was related to medication intake.

Types of Studies Reviewed. The search covered a period from January 1, 1965, to September 29, 2014. The search revealed 1,042 articles, to which the authors applied eligibility criteria and selected 20 studies for review. The authors considered 9 of the 20 studies to be high quality. The drugs used in these studies were chemotherapeutic drugs, antibiotics, asthma drugs, antiepileptic drugs, antiviral drugs, antifungal drugs, and antiparasitic drugs.

Results. Two reviewers independently performed risk-of-bias assessment and data extraction. The investigators of all of the studies had reported enamel defects, but only 2 sets of investigators had used the term "molar incisor hypomineralization." Owing to the different methodologies used by the investigators of the selected studies, the authors could not perform a meta-analysis of the study results.

Conclusions. More well-designed prospective studies are needed to clarify the relationship between MIH and medication.

Practical Implications. It would be convenient to establish a preventive protocol in patients with a potential risk of developing MIH to avoid the complications that are characteristic of this disease.

Key Words. Enamel hypoplasia; enamel opacities; enamel defects; enamel hypomineralization; molar incisor hypomineralization; drugs.

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Dental enamel is a highly mineralized tissue of ectodermal origin that, once formed, is characterized by a lack of metabolic activity. This means that any disturbance during its formation may manifest as a permanent defect in the erupted tooth.[1]

Defects can be classified as hypoplasia (quantitative defect) or hypomineralization (qualitative defect), depending on when the disturbance took place. For example, a disturbance that occurs during the secretory stage of amelogenesis would translate into hypoplasia, whereas an aggression that occurs during the transitory or maturation stage would result in hypomineralization.[2-4]

Molar incisor hypomineralization (MIH), a syndrome described in 2003 by Weerheijm[5] as a qualitative, idiopathic defect that affects mainly permanent first molars but also incisors, can be diagnosed once these teeth have erupted.[6,7] Elfrink and colleagues[8] described decidious molar hypomineralization (DMH), which affects primary second molars and is considered to be a predictive factor for MIH. Both MIH and DMH are considered to be qualitative defects of enamel that manifest in white, yellow, or brown opacities depending on the degree of the defect.

According to the results of the studies we consulted,[9,10] the prevalence of MIH varies widely, ranging from 2.4% in Germany to 40.2% in Rio de Janeiro, Brazil. However, the different methodologies used by authors, the differences in diagnostic criteria, and the bias associated with the populations studied (for example,

different age ranges and lack of any clear representative population) make it difficult to establish the exact prevalence of MIH.[9,10]

MIH leads to increased concentrations of proteins and a lower enamel mineral content than in normal teeth. The proteins found include serum albumin, type I collagen, ameloblastin, α1-antitrypsin, and antithrombin III. Some of these proteins inhibit the growth of hydroxyapatite crystals, and others interfere with the enzymatic activity of kallikrein 4. The level of amelogenins remains normal, which differentiates the enamel of teeth with MIH from the enamel of teeth with hypomaturation, typical of amelogenesis imperfecta and fluorosis, which contain high levels of amelogenins.[11] The mineral content of MIH enamel is reduced by approximately 20%, a percentage that gradually decreases from the amelodentinal junction toward the most superficial enamel. Similarly, the hardness and elasticity module of the enamel gradually decreases.[12]

Hypomineralized enamel is more fragile and porous than normal enamel, which means that a tooth with hypomineralized enamel has an increased risk of developing caries. Posteruptive enamel breakdown is common owing to chewing forces; dentin tubules are exposed, and there is chronic pulpitis and a high level of dental sensitivity. This results in pain that is difficult to control during restorative treatment, along with the corresponding difficulty of managing children's behavior during the application of dental treatment.[4,5,11]

Although many factors have been associated with the etiology of MIH, the cause of MIH still remains relatively unknown. The disorder has been associated with prenatal, perinatal, and postnatal factors.[13,14] Concerning postnatal factors, the use of drugs during the first 4 years of life is considered one of the main causes. Even before the European meeting in Athens, Greece,[15] when this syndrome took on a definitive name, investigators had associated several drugs with enamel defects, although they had not referred to the condition as MIH. However, it is possible that the investigators were referring to the condition that was later named MIH because the enamel defects described in the literature had similar characteristics of demarcated opacities and posteruptive breakdown.[15]

To date, no investigators have published a literature review on the relationship between drugs and MIH.

The purpose of our systematic review was to summarize the knowledge about the association between MIH and the use of drugs during pregnancy and the first 4 years of life. Specifically, we addressed the following questions:

- What is the possible association between medication intake during pregnancy and MIH?
- What is the possible association between medication intake during the first 4 years of life and MIH?

Using the components of the Patient, Intervention, Comparison, and Outcome (PICO) system,[16] we outlined the aims of our systematic review as follows:

- P: The patient population (or problem) we addressed were the children exposed to drugs during pregnancy and the first 4 years of life.
- I: The intervention or exposure of interest were the drugs to which the participants were exposed.
- C: The comparators were the control groups of the studies.
- O: The main outcome or endpoint of interest was the relationship between drug exposure and MIH.

METHODS

We performed this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement,[17] and we registered our review as CRD42014014778 in the Centre for Reviews and Dissemination, University of York, York, United Kingdom.

Study selection criteria. According to the selection criteria, in this review we included articles whose authors had described cohort, case-control, and cross-sectional studies as well as randomized clinical trials whose authors had evaluated the association between MIH and drug administration during pregnancy or the first 4 years of life. We excluded animal studies, case reports, pilot studies, editorials, letters, and literature reviews. We included studies that described outcomes in both primary and permanent dentition.

Search strategy and screening of articles. Without specifying that an article had to be published in a specific language, we conducted a detailed search in the following electronic databases: PubMed, Pharmaceutical News Index, MEDLINE, MEDES, Cochrane Library, and Embase. The search covered a period from January 1, 1965, to September 29, 2014. We covered all tooth-related terms by using the following search string and making alterations as appropriate for the various database requirements: "dentition," "tooth," "teeth," "dental enamel," "enamel hypoplasia," "enamel opacities," "enamel defects," "enamel hypomineralization," and "molar incisor hypomineralization" combined with the terms "drugs," "antibiotics," "antinflammatories," "asthma drugs," "inhalers," "chemotherapy," "chemotherapeutic drugs," "corticoids," "antipyretics," "analgesics," "antiviral drugs," "antifungal," and "antiparasitic."

We performed the selection of the studies in 3 stages (Figure). In stage 1, we considered only the title. In stage 2, we considered the abstract. If the abstract did not provide sufficient information for us to make a decision

ABBREVIATION KEY. **DDE:** Developmental Defect of Dental Enamel. **DMH:** Decidious molar hypomineralization. **FRI:** Fluorosis Risk Index. **MIH:** Molar incisor hypomineralization. **NOS:** Newcastle-Ottawa Quality Assessment Scale. **NS:** Not significant.