Review Article

**Impact of medication use on the development of enamel defects in childhood: a critical review**

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**ABSTRACT**

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| **Aims:** This review critically evaluated the scientific evidence regarding the association between medication exposure during pregnancy or early childhood and the development of developmental enamel defects (DDEs) in children.  **Study design:** Critical literature review  **Place and Duration of Study:** Sample: Department of Medicine (Medical Unit IV) and Department of Radiology, Services Institute of Medical Sciences (SIMS), Services Hospital Lahore, between June 2009 and July 2010.  **Methodology:** A systematic search was conducted across six databases and the gray literature, following PRISMA guidelines and registered in PROSPERO (CRD420251047079). Observational cohort studies published from 2001 onward were included. Study quality was assessed using the Newcastle-Ottawa Scale (NOS).  **Results:** Of 1,362 records initially retrieved, 10 cohort studies met the inclusion criteria. No randomized clinical trials were found. The studies investigated various medications, including antibiotics, corticosteroids, asthma drugs, antivirals, bisphosphonates, and vitamin D supplements. While some studies reported associations—particularly with amoxicillin and molar-incisor hypomineralization (MIH)—others found no statistically significant links. NOS scores ranged from 6 to 9 stars, indicating moderate to high methodological quality. Although causal relationships could not be established, observational studies remain a viable approach for investigating the potential impact of medications on dental development.  **Conclusion:** Findings support the need for well-designed cohort studies with standardized diagnostic protocols to guide future research and public health strategies in pediatric dentistry. |

*Keywords: Pediatric dentistry; developmental defects of enamel; child; anti-bacterial agents.*

**1. INTRODUCTION**

Developmental defects of enamel (DDE) are qualitative alterations, such as hypomineralization, or quantitative changes, such as hypoplasia, that occur during enamel formation (Santos and Abreu, 2024). These anomalies can lead to dental sensitivity and pain, compromising eating, oral hygiene, and school performance (Costa, 2024), in addition to increasing susceptibility to primary caries and the need for invasive treatments (Portella et al., 2022). Dental aesthetics are also affected, which may harm self-esteem and hinder social interaction, thereby negatively impacting children’s quality of life (Cunha et al., 2020; Oliveira et al., 2024; Silva et al., 2021).

Although DDEs have been scientifically recognized for over a century, their etiological mechanisms remain poorly understood (Becam and Chevalier, 2019). Current evidence suggests a multifactorial origin, involving systemic disorders, genetic factors, environmental exposures, and the use of medications during critical phases of enamel formation (Dulla and Meyer-Lueckel, 2021; Inchingolo et al., 2023).

In 2001, the European Academy of Paediatric Dentistry Consensus formally defined Molar–Incisor Hypomineralisation (MIH) as a qualitative condition of systemic origin, characterized by demarcated opacities (ranging from white-cream to yellow or brown) that affect at least one first permanent molar and often incisors, reflecting a defect in the final enamel maturation process (Weerheijm et al., 2003). A bibliometric study identified a significant increase in MIH-related publications in the past decade, most of which were observational studies (39%). The most discussed topics included the condition’s prevalence and incidence, potential systemic etiological factors, and treatment options (Soares et al. 2024).

Exposure to certain medications during critical periods of dental development is recognized as a significant etiological factor associated with DDEs (Dulla, 2021; Mazur, 2023). Evidence from the literature suggests a higher prevalence of these defects among children exposed to medications such as antibiotics and corticosteroids during pregnancy or early childhood (França et al., 2021; Garot et al., 2022; Mastora et al., 2017).

Studies suggest that antibiotics such as amoxicillin and cefaclor, when administered during pregnancy or early childhood, may interfere with enamel formation, leading to structural defects (Laisi, 2009; Hong, 2011; Arjona, 2018). Moreover, the use of inhaled drugs for asthma treatment during childhood, especially in the preschool years, appears to be associated with an increased risk of enamel defects in first permanent molars (Mastora et al., 2017).

Conversely, some studies have indicated that the use of vitamin D during pregnancy may have a protective effect on children’s oral health. One such study by Nørrisgaard et al. (2019) suggests that vitamin D plays an important role in odontogenesis, particularly in ameloblast differentiation and enamel mineralization regulation. This line of evidence was reinforced by Tapalaga et al. (2023), whose review of seven studies—including data from 6,978 participants—found that adequate vitamin D levels during pregnancy were associated with a lower frequency of conditions such as hypomineralization, hypoplasia, and even dental erosion in both primary and permanent teeth.

Although some studies report a strong correlation between the use of antibiotics, corticosteroids, and inhaled agents and the occurrence of enamel defects (Arjona, 2018; Garot et al., 2022; Mastora et al., 2017), the growing number of studies on this association still presents inconclusive and often contradictory results. Moreover, several investigations have not found statistically significant relationships between childhood medication use and the development of enamel defects (Muñoz et al., 2020; Wogelius, Viuff, Haubek, 2020).

Thus, this literature review aims to synthesize and critically evaluate the available evidence on the relationship between medication exposure and the development of enamel defects in childhood, thereby contributing to clinical practice and the formulation of public health policies.

**2. methodology**

**2.1 Protocol and Registration**

This review was conducted in accordance with the recommendations described in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was registered in PROSPERO (International Prospective Register of Systematic Reviews) under registration number CRD420251047079.

**2.2 Search Strategy**

The research question was structured using the PICOS strategy, which includes five essential components: P – population, I – intervention, C – comparison, O – outcome, and S – study design. Accordingly, the following question was formulated: “Is exposure to medications during pregnancy or early childhood associated with the development of enamel defects in children?”

The target population consisted of children aged 0 to 12 years who were exposed to medications either during the prenatal period—via maternal exposure—or within the first five postnatal years, a phase considered critical for odontogenesis and the formation of both primary and permanent enamel.

As for the intervention or exposure, this included the use of medications such as antibiotics, corticosteroids, antipyretics, anti-inflammatory drugs, antivirals, antifungals, antiparasitics, and vitamins. The comparator group comprised children in the same age range who had not been exposed to these medications.

Regarding the outcome, the focus was on the presence of developmental enamel defects (DDE), including hypoplasia, hypomineralization, and opacities. Although randomized clinical trials were initially defined as the preferred study design, none were found on the topic. Therefore, high-quality cohort studies were selected for inclusion in this review.

**2.3 Eligibility Criteria**

This review included observational cohort studies (prospective or retrospective), published from 2001 onwards, in any language. Initially, no restrictions were applied regarding the year of publication during the search phase, respecting the principles of comprehensiveness and sensitivity. However, during the full-text screening of eligible studies, it became necessary to establish a time cutoff starting in 2001. This decision was based on the diagnostic standardization of MIH, formalized by the European Academy of Paediatric Dentistry consensus in 2001, which brought greater methodological uniformity to studies published thereafter (Weerheijm et al., 2003).

**2.4 Databases and Descriptors**

The search was conducted on May 20, 2025, in the following databases: Medline (via PubMed), Cochrane Library, Web of Science, Scopus, Virtual Health Library and Embase. A gray literature search was also performed by screening the first 100 references retrieved on Scholar Google. The descriptors were selected based on MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors) vocabularies, including terms such as “Developmental Defects of Enamel”, “Pediatric Dentistry”, “Hypoplasia”, “Antibiotics”, “Corticosteroids”, “Medications”, among others relevant to the research topic, combined or not.

**2.5 Study Selection**

The search, study selection, and data extraction processes were conducted independently by two reviewers (IDCF, GLP), ensuring methodological rigor. Discrepancies were resolved with the assistance of a third reviewer, ensuring accuracy and reliability in the analysis. After the electronic search, the references were exported to the Rayyan Systematic Review reference manager. Duplicates were removed, and the titles and abstracts were screened. In the next stage, the selected studies were read in full and assessed according to the study’s eligibility criteria.

**2.6 Data Extraction and Risk of Bias Assessment**

A thorough and detailed analysis of the selected articles was performed, carefully evaluating the specific characteristics of each study. Information collected included authorship, year and country of publication, study design, sample size, children's age, objectives, inclusion and exclusion criteria, interventions, and main findings.

The methodological quality of observational cohort studies (both prospective and retrospective) was independently assessed by two reviewers (JAS and JLV) using the Newcastle–Ottawa Scale, developed by Wells et al. (2015). This tool is widely used to assess the quality of observational studies, particularly cohort and case-control designs, and is recommended by institutions such as the Cochrane Collaboration (Stang, 2010; Bitencourt et al., 2021; Cochrane, 2021; Reeves, 2021).

This assessment is based on three fundamental domains: selection of participants, comparability of groups, and outcome assessment. Each domain is scored using a star system, based on specific criteria, and a total score is calculated, with a maximum possible score of nine stars.

The selection domain evaluates aspects such as the representativeness of the cohort, the adequacy of the non-exposed group, the method of exposure ascertainment (via reliable records or self-report), and confirmation that the outcome was not present at baseline. A maximum of four stars can be awarded in this domain.

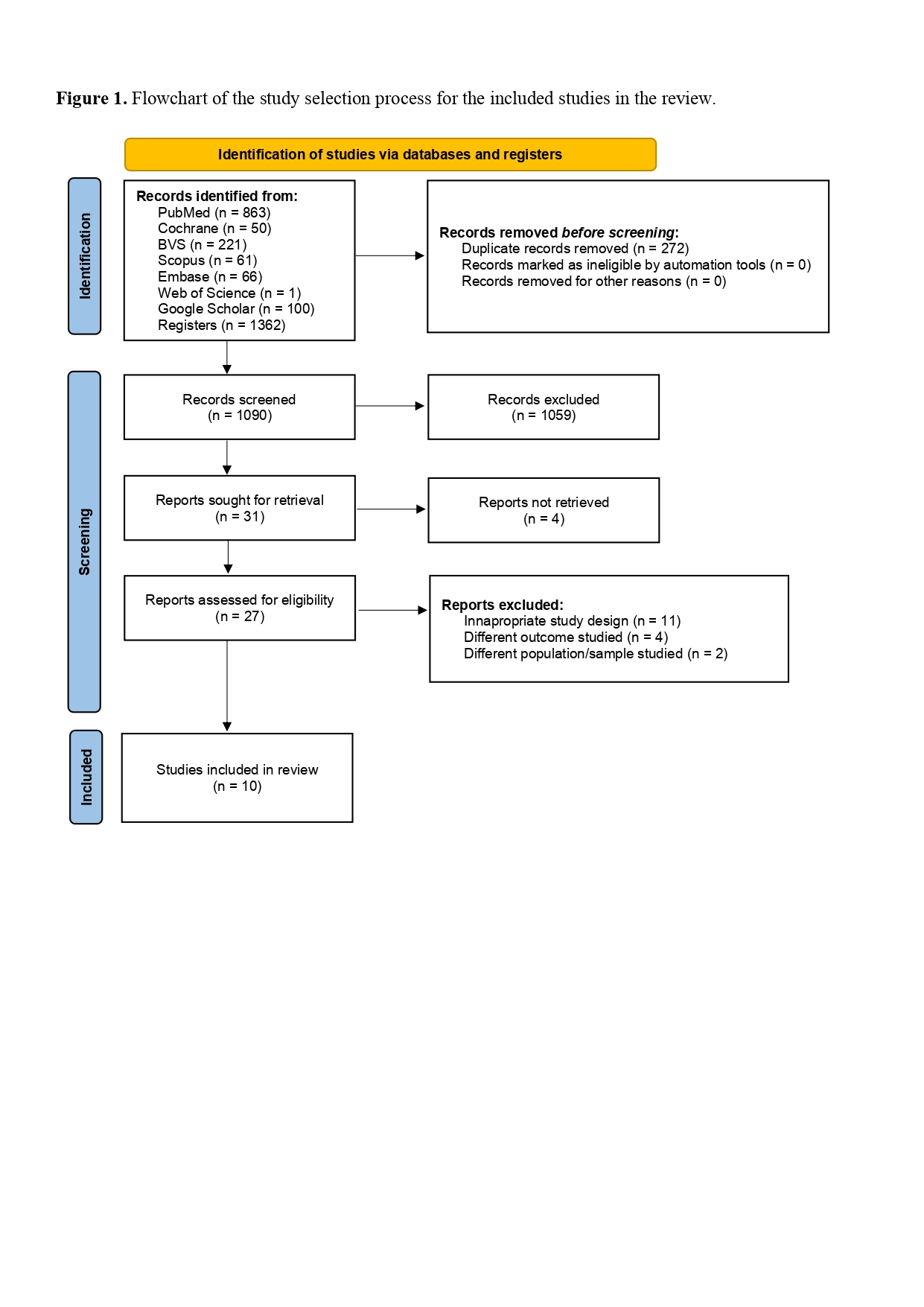
For the comparability domain, the focus is on whether the study controlled for the main confounding factor and other relevant variables, using strategies such as matching, stratification, or multivariate analysis. This domain allows for a maximum of two stars.

Lastly, the outcome domain considers the adequacy of outcome assessment (preferably performed by blinded examiners or through standardized records), the follow-up period's sufficiency for the outcome to occur, and whether any losses to follow-up were acceptable and properly justified. Up to three stars can be awarded in this domain (Wells et al., 2015).

After independent domain assessments, the reviewers reached a consensus and defined the final methodological quality scores for the included cohort studies.

**3. results**

The systematic search across databases yielded a total of 1,362 records. After removing 272 duplicates, 1,090 titles and abstracts were screened, from which 31 articles were selected for full-text reading. Following the application of the eligibility criteria, 10 studies were included in this review, as illustrated in the PRISMA flowchart (Figure 1).



**Fig. 1. Flowchart of the study selection process for the included studies in the review**

A synthesis of the included studies is presented in Table 1. The search identified 10 cohort studies. Specifically, 3 studies used retrospective cohorts and 7 used prospective cohorts; no randomized controlled trials were found. These studies assessed the use of antibiotics, anti-asthmatic drugs, antivirals, bisphosphonates, and cancer therapies, in addition to perinatal factors, considering outcomes such as fluorosis, developmental defects of enamel, molar-incisor hypomineralization, and other dental anomalies. The findings revealed variability in the reported associations between medication exposure and the observed dental alterations.

**Table 1. Data synthesis**

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| **Author/Year/**  **Country/Study type** | **Sample size** | **Objective** | **Inclusion criteria** | **Assessments** | **Conclusion** | |
| Hong *et al.*,  2004 / USA  Prospective cohort | 490 children | Investigate the association between amoxicillin in the first year of life and the occurrence of fluorosis in primary teeth | Children born between 1992–1995 with data on antibiotic and fluoride use during the first year | Periodic questionnaires and dental examination to assess TSIF at age 5 | Fluoride was the strongest predictor of fluorosis. Amoxicillin may be a contributing factor. | |
| Hong *et al.*,  2005 / USA  Prospective cohort | 579 children | Evaluate the association between amoxicillin in use the first year of life and DDE, focusing on fluorosis in early-erupting  permanent teeth | Children born between 1992–1995 with complete data on antibiotic use | Periodic questionnaires; assessment of fluorosis in permanent central incisors and molars at age 9 using the FRI | Results suggest a link between childhood amoxicillin use and DDE in permanent teeth (fluorosis in upper central incisors and 1st PM) | |
| Hong *et al.,*  2011 / USA  Prospective cohort | 357 children | Assess whether early childhood use of amoxicillin is associated with fluorosis in late-erupting permanent teeth | Children born between 1992–1995 with complete antibiotic use data | Amoxicillin use assessed by questionnaires up to 32 months; fluorosis assessed at age 13 using FRI | Early childhood use of amoxicillin may be a risk factor for fluorosis in late-erupting permanent teeth | |
| Elfrink *et al.*,  2013 / Netherlands  Prospective cohort | 6.690 children | Investigate whether antibacterial, antiallergic, and antiasthmatic drugs are associated with dMIH | Data on maternal medication use during pregnancy; photos of children's primary molars | Exposure assessed via pharmacy records; dmHMI diagnosed from photographs using EAPD criteria | No significant association between maternal medication use during pregnancy and dmHMI | |
| Owosho *et al.,*  2016 / USA  Retrospective cohort | 13 children | Investigate long-term effects of Chemo-IMRT on dentofacial development in HNRMS survivors | Diagnosis of HNRMS; treatment with Chemo-IMRT; ≥5 years post-treatment survival | Evaluation from medical records and radiographs: hypoplasia, dental agenesis, root anomalies, trismus, and xerostomia | Despite IMRT, dentofacial abnormalities persisted, especially in children ≤ 7 years old | |
| Kühnisch *et al*., 2017 / Germany  Prospective cohort | 406 children | Analyze the association between fluoride and vitamin D supplementation in the first year of life and dental status, including caries and MIH at age 10 | Healthy children with available data on supplementation during the first 12 months | Dental examination assessing caries, treatments in permanent teeth, and MIH presence | Fluoride and vitamin D supplementation in infancy: lower risk of caries in primary dentition. No significant effect on permanent teeth or MIH | |
| Schüttfort *et al.*, 2020 / Germany  Prospective cohort | 31  children | Assess whether intrauterine exposure to TDF in HIV-exposed but uninfected children is associated with DDE in primary dentition | HIV-exposed, uninfected children whose mothers received TDF for ≥ 4 months in pregnancy | Dental exam, mDDE index, questionnaire, and comparison with unexposed cohorts | Intrauterine TDF exposure: no significant increase in DDE prevalence or distribution | |
| Malmgren *et al.,* 2021 / Sweden  Retrospective cohort | 219 children | Evaluate the effect of early BP therapy for OI on the development / mineralization of permanent teeth | Confirmed OI diagnosis and complete medical records of bisphosphonate use | Clinical examination; photographic and radiographic evaluation | BP initiation before age 2 significantly increases the risk of dental anomalies and enamel defects | |
| Raedel *et al.,*  2022 / Germany  Retrospective cohort | 298.502 children | Investigate the association between early childhood medication exposure and MIH occurrence, potential influence of perinatal factors | Children with continuous data from birth to age 9 and insured between 6–9 years (MIH diagnosis) | MIH diagnosis based on treatment patterns in first molars; medication prescription records from the first 4 years of life | Early antibiotic use may be associated with higher MIH prevalence; no association found with perinatal factors | |
| Nørrisgaard *et al.,* 2023 / Denmark  Prospective cohort | 700  mother-  child  pairs | Evaluate whether asthma and its treatments increase the risk of caries and enamel defects by age 6 | Participants of the COPSAC2010 cohort; routine medical supervision and symptom diaries | Medication use, asthma diagnosis during pregnancy and infancy; dental exam at age 6 (caries and DDE) | Asthma medication use in the first 6 years was not associated with caries development or  DDE at age 6 | |
| Source: adapted from Silva et al., 2024, Muniz et al., 2025, Protásio et al., 2025. . Abbreviations: **1st PM** = First Permanent Molar; **AF** = Sickle Cell Anaemia; **BP** = Intravenous Bisphosphonate; **Chemo-IMRT** = Chemotherapy with Intensity-Modulated Radiotherapy; **DDE** = Developmental Defects of Enamel; **DE** = Enamel Defect; **DGI** = Dentinogenesis Imperfecta; **dMIH** = Deciduous Molar Hypomineralization; **DP** = Permanent Teeth; **FRI** = Fluorosis Risk Index; **HNRMS** = Head and Neck Rhabdomyosarcoma; **MIH** = Molar-Incisor Hypomineralization; **mDDE** = modified Developmental Defects of Enamel index; **MP** = Permanent Molar; **OI** = Osteogenesis Imperfecta; **TDF** = Tenofovir; **TSIF** = Tooth Surface Index of Fluorosis. | | | | | | |

Based on the three predefined domains used to assess methodological quality according to the Newcastle-Ottawa Scale (NOS), the risk of bias among the included cohort studies ranged from moderate to high. Of the 10 cohort studies included, 3 received the maximum score of 9 points, 1 received 8 points, 4 received 7 points, and 2 scored 6 points according to the NOS (Table 2).

**Table 2. Assessment of methodological quality of cohort studies**

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| **Author / Year/**  **Study design** | **Selection** | **Comparability** | **Exposure / Outcome** | **Score** |
| Hong *et al.*, 2004  Prospective cohort | \*\*\* | \*\* | \*\* | 7 |
| Hong *et al.*, 2005  Prospective cohort | \*\*\* | \*\* | \*\* | 7 |
| Hong *et al.,* 2011  Prospective cohort | \*\*\* | \*\* | \*\* | 7 |
| Elfrink *et al.*, 2013  Prospective cohort | \*\*\*\* | \*\* | \*\* | 8 |
| Owosho *et al.,* 2016  Retrospective cohort | \*\* | \*\* | \*\* | 6 |
| Kühnisch *et al*., 2017  Prospective cohort | \*\*\* | \*\* | \*\* | 7 |
| Schüttfort *et al.*, 2020  Prospective cohort | \*\* | \*\* | \*\* | 6 |
| Malmgren *et al.,* 2021  Retrospective cohort | \*\*\*\* | \*\* | \*\*\* | 9 |
| Raedel *et al.,* 2022  Retrospective cohort | \*\*\*\* | \*\* | \*\*\* | 9 |
| Nørrisgaard *et al.,* 2023  Prospective cohort | \*\*\*\* | \*\* | \*\*\* | 9 |
| Source: adapted from Dreweck et al., 2020. | | | | |

**4. discussion**

This review did not identify randomized controlled trials (RCTs) addressing the research question: “Is exposure to medications during pregnancy or childhood associated with the development of enamel defects in children?” However, seven prospective cohort studies and three retrospective cohort studies were identified that explored the potential association between medication intake and the occurrence of enamel defects in children.

The absence of RCTs is likely due to the ethical challenges involved in conducting clinical trials with pregnant women and children, especially considering the potential harm associated with drug exposure (Sheffield et al., 2014; Van Der Graaf et al., 2018). A recent survey indicated that, among nearly 400.000 clinical studies registered on ClinicalTrials.gov, fewer than 9.000 included pregnant women, with the vast majority being observational studies due to legal concerns and historical medication-related harms in this group (Shaikh et al., 2024).

Moreover, the long interval between exposure and the onset of enamel defects makes the execution and follow-up of RCTs logistically unfeasible, particularly due to potential loss to follow-up and even mortality during extended monitoring periods. As a result, many researchers rely on observational designs, such as cohort or case-control studies (Herbert; Kasza; Bø, 2018).

In recent years, the traditional hierarchy of the evidence pyramid has been reconsidered in light of the practical and ethical limitations of conducting RCTs. While RCTs remain the gold standard for establishing causality, well-designed observational studies have gained recognition for their relevance and clinical applicability (Murad et al., 2016). Thus, when addressing associations between medication exposure and enamel defects, the cohort studies included in this review play a central role and meaningfully contribute to building reliable knowledge, even in the absence of controlled trials.

Studies with a score of six stars on the Newcastle-Ottawa Scale (NOS) generally indicate moderate methodological quality, partially meeting the assessment criteria and showing limitations that may affect internal or external validity (Canto, 2021). In this review, studies with this score exhibited follow-up losses or lacked clear descriptions of cohort retention, sample representativeness, and the selection of the non-exposed cohort (Schüttfort et al., 2020; Owosho et al., 2016). These limitations suggest a moderate risk of bias, especially regarding the generalizability of findings and the robustness of observed associations.

All studies scoring below nine stars received no points in the domain assessing adequacy of cohort follow-up due to significant attrition or lack of clear information regarding losses (Hong et al., 2004a, 2005b, 2011c; Kühnisch et al., 2017; Elfrink et al., 2013; Schüttfort et al., 2020; Owosho et al., 2016). This limitation may compromise the reliability of outcomes and must be considered when interpreting the results. Nonetheless, the NOS proved effective in distinguishing the methodological quality of the included studies. While most studies were of good quality, variability was noted in follow-up rigor and reporting of losses, reinforcing the importance of transparency and completeness in study design.

Compared with the findings of the systematic review by Serna et al. (2016), which evaluated studies published up to 2014 regarding the association between medication use in childhood and MIH occurrence, the cohort studies included in the present review scored higher and more consistently on the NOS. This may reflect improved methodological standards in more recent investigations, as the highest-quality studies in this review were also the most recent (Schüttfort et al., 2020; Raedel et al., 2022; Nørrisgaard et al., 2023).

No consistent relationship was found between NOS score and the type of cohort study. Both prospective and retrospective cohorts scored similarly, ranging from six to nine stars. Although prospective designs are theoretically more robust (Salazar et al., 2019), some retrospective studies in this sample demonstrated comparable or even superior methodological quality. Therefore, NOS scoring appears to depend more on design quality and bias control than on study type, and each study should be interpreted in light of its specific context (Wells et al., 2015).

Among the medications assessed, amoxicillin was the drug most frequently associated with enamel defects. Prospective cohort studies by Hong et al. (2004a, 2005b, 2011c) in the United States suggested a possible link between amoxicillin use during the first year of life and the development of dental fluorosis and enamel defects in both primary and permanent teeth. Laisi et al. (2009) supported this hypothesis, identifying early amoxicillin use as a potential causal factor in MIH. More recently, Raedel et al. (2022) reinforced this association, reporting a higher prevalence of MIH in children with early antibiotic exposure, including amoxicillin. Although the effects of this specific antibiotic were not isolated, its frequent prescription and potential role in enamel mineralization defects were considered relevant by the authors (Raedel et al., 2022).

Conversely, conflicting results are found in the literature. Elfrink et al. (2013), for example, reported no statistically significant association between the use of antibacterial drugs during pregnancy and the development of enamel hypomineralization. These discrepancies may result from methodological differences, including how exposure was measured, variations in outcome definitions (e.g., fluorosis, hypoplasia, or MIH), or insufficient control for confounding factors such as fluoride intake and genetic susceptibility.

Regarding systemic medications, the study by Owosho et al. (2016) was the only one found to investigate cancer treatment in relation to enamel defects. The authors reported that children with head and neck rhabdomyosarcoma treated with radiotherapy and chemotherapy exhibited dentofacial abnormalities. This aligns with other studies reporting associations between chemotherapy and enamel defects (Kaste et al., 2009; Bagattoni et al., 2014).

However, Nørrisgaard et al. (2023) found no association between asthma medication use and enamel defects in children—contrasting with Mastora et al. (2017), who reported a general increased risk of hypomineralization in first permanent molars among children treated with asthma medications.

The role of vitamin D supplementation during pregnancy remains unclear due to conflicting findings. Nørrisgaard et al. (2019) found that high-dose supplementation significantly reduced the occurrence of enamel defects in children. Similarly, Colonetti et al. (2022) emphasized that adequate prenatal vitamin D levels may benefit both oral and systemic health. Observational studies such as Børsting et al. (2022) and the systematic review by Tapalaga et al. (2023) further suggested that insufficient maternal vitamin D is associated with an increased prevalence of these defects. Nevertheless, Kühnisch et al. (2017) reported no significant effect of postnatal fluoride and vitamin D supplementation on MIH, and Rogalnikovaite et al. (2022) highlighted that the effects of prenatal vitamin D on oral health remain inconclusive. While causal evidence is lacking, the body of findings points to a potential role for vitamin D in dental formation.

The main limitations of this review stem from the scarcity of RCTs in the literature, for the ethical and practical reasons previously discussed. Although RCTs represent the highest level of clinical evidence, the lack of controlled trials should not be interpreted as an absence of association (Brasil, 2014). On the contrary, it highlights the importance of considering alternative designs—such as well-conducted prospective and retrospective cohort studies—which allow for ethical and longitudinal assessment of drug exposure effects on children’s oral health (Serna et al., 2016). Given the heterogeneity in findings, a synthesis of high-quality observational evidence remains critical. While some studies reported significant associations between medication use and enamel alterations (Jacobsen et al., 2023; Shinde et al., 2022), others did not find statistically significant results (Schüttfort et al., 2020; Elfrink et al., 2013).

Therefore, future investigations should prioritize cohort designs with representative samples, long-term follow-up, and standardized diagnostic protocols for enamel defects. Multicenter studies involving diverse populations may further enhance the evidence base and support public health policies.

One of the main strengths of this review lies in its comprehensive search strategy across relevant databases. This methodological rigor provides an updated and broad perspective on the topic, reducing the risk of publication bias (Wells et al., 2015; Brasil, 2014). Another strength was the use of strict inclusion criteria and a standardized methodological assessment using the Newcastle-Ottawa Scale, which allowed prioritization of evidence quality. This critical approach enhances the reliability and clinical relevance of the findings while offering solid directions for future research in pediatric oral health.

**4. Conclusion**

Observational studies investigating the potential association between medication use and enamel developmental defects were identified. However, the available evidence does not allow for the establishment of a direct causal relationship between drug exposures and the occurrence of enamel defects. In the absence of randomized controlled trials, these studies remain a viable alternative for exploring this topic, supporting future research, clinical practice, and public health policy focused on child health.

**Consent**

It is not applicable

**Ethical approval**

It is not applicable

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