







# Clinical and Molecular Disorders Caused by COVID-19 During Pregnancy as a Potential Risk for Enamel Defects

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## ABSTRACT

This paper discusses the potential risk that COVID-19 generates for the development of enamel defects. This hypothesis was built based on the etiopathogenesis of enamel defects and the relationship with the symptom's characteristic of COVID-19. Pregnancy is a critical period for the child's development; exposure to pathological agents can cause systemic imbalances and risks of adverse perinatal and prenatal outcomes. The main clinical symptoms of this disease and its association with that dental outcome were considered. Fever, breathing, cardiovascular disorders, and diarrhea were related as potential etiological factors of ameloblast metabolism imbalance, which can interfere qualitatively and quantitatively in the development, maturation and mineralization of the tooth enamel. Molecular disorders derived from COVID-19, as well as their clinical symptoms, can be considered potential risk factors for the development of enamel defects. Individuals with enamel defects experienced high stress levels during pregnancy or early childhood. The approach adopted may help build new research to ensure understanding of the etiology of the development of dental enamel defects and its relationship with COVID-19. However, longitudinal studies need to be conducted to confirm the association between COVID-19 and adverse events during pregnancy.

**Keywords:** COVID-19; SARS-CoV-2; Dental Care; Dental Enamel; Child; Pregnancy.

## Introduction

Adverse events occurring prenatally, perinatally, and during birth may determine an individual's oral health [1]. Pregnancy is a critical period for the child's development. Physiological changes in pregnancy increase susceptibility to infections due to an imbalance in the immune system, increased concentrations of inflammatory proteins, activation of hypercoagulability status, deduction of oxygen deficiency tolerance and cardiovascular adaptations by hormonal action [2,3].

International centers for disease control and prevention are monitoring this infectious disease outbreak; symptoms of COVID-19 infection include fever, cough, and acute respiratory disease, with severe cases leading to pneumonia, kidney failure, and even death [4]. The literature has reported the clinical symptoms of COVID-19 as a hyper inflammation or cytokine storm [5]. Other diseases with inflammatory characteristics, oxidative stress or endothelial dysfunction during pregnancy, such as preeclampsia, are associated with adverse perinatal outcomes [6].

The formation and maturation of deciduous teeth are susceptible to maternal metabolic imbalance; thus, the tooth enamel can act as a biological marker, thanks to the lack of tissue remodeling throughout the life of an individual, with alterations occurring during its formation being permanently detectable [7,8]. The mechanisms that link pathophysiological disorders with enamel hypoplasia are varied. Individuals with enamel defects experienced high-stress levels during pregnancy or early childhood [9].

## Amelogenesis

The amelogenesis, the process of forming dental enamel, begins in the 15th week of intrauterine life. Most of it is formed during the prenatal stage, and throughout childhood [1,10]. This may suggest that contamination by COVID-19 in this period can generate defects in the formation of tooth enamel. Etiology of enamel's developmental defects, there are numerous hereditary, acquired, systemic, and local etiological factors associated with enamel defects [11,12]. Ameloblasts are cells sensitive to physiological or pathological variations in pregnancy. The symptoms of COVID-19 are known to disturb these cells, causing disorder in the secretion of the protein matrix or interfering with these cells' metabolism [13]. These disbalance can generates defective enamel qualitatively or quantitatively in deciduous teeth [14]. In this point of view, we discuss the potential risk that COVID-19 generates for the development of enamel defects. Thus, the main symptoms of this disease and its association with such an outcome was considered.

- Fever – A common symptom of infection is fever and, therefore, its role is difficult to distinguish from that of the disease itself. Viral and bacterial infections have been reported as possible etiological agents of enamel defects, such as: zika syndrome, chickenpox, cytomegalovirus, measles, rubella, syphilis, respiratory and gastrointestinal infection [14-16]. High fever has been reported to cause enamel defects [17]. Altered expression of genes important in enamel formation has also been suggested as the link between fever and enamel defects [18] from this perspective, processes of gene Modulations in microRNA, DNA methylation and chromatin modifications are emerging as important regulatory mechanisms during tooth development [19]. Alternatively, the etiology may relate to a metabolic disturbance described in rat studies showing that acidic conditions (a result of both localized inflammation and hypoxia) can prevent crystal growth due to the build-up of hydrogen ions [20]. Although the literature has reported that high fever in childhood establishes a relationship with enamel defect [14,17], fever that occurs during pregnancy, especially during the formation and maturation of the enamel matrix







can generate the same damage since the principle of the process itself it does not differ in relation to the moments of occurrence. It is also known that adverse events that occur in earlier stages of odontogenesis culminate in worse results [21].

- Breathing disorders - After infection and wide viral replication of this disease in the epithelial cells of the respiratory system, imbalances in the immune response with leukocyte damage have been identified, especially in auxiliary and regulatory T lymphocytes that play an important role in immune homeostasis and the prevention of an exacerbated inflammatory response [22,23]. The imbalance between the immune system and the respiratory system makes this characteristic critical for ameloblasts, sensitive to external variations and oxidative processes derived from inflammation and fever. Oxygen deficiency during childbirth or pregnancy has been reported as a possible metabolic disorder acting on odontoblasts, resulting in the formation of abnormal tissue [24]. The reduced oxygen levels may lead to dental enamel matrix secretion disorders due to the detrimental influence on the cellular metabolism of ameloblasts [25]. The literature has associated pneumonia and asthma at a very early age and enamel defects incidence [14,17]. Therefore, the hypothesis that this symptom of COVID-19 in pregnant women may interfere with tissue formation mechanism seems to be imminent. However, future studies need to prove this relationship.
- Cardiovascular disorders - Clinically, the characteristic pulmonary impairment of COVID-19 has contributed to increased in cardiac and laboratory demand and has been identified as an increase in myocardial tissue injury markers [26]. The COVID-19 course demands exaggerated inflammation, endothelial lesions, and the potential risk of organs' involvement, directly and indirectly, related to the cardiovascular system [27]. Such occurrences, at the cellular level, can generate disturbances in the metabolism of ameloblasts that produces damaged protein matrix and consequently enamel defects in children.
- Diarrhea - Although it appears as a less frequent event in covid-19, diarrhea in pregnancy, when severe, can be a potential risk for the development of enamel defects in children as it causes deficiencies in macro and micronutrient absorption. The enamel tissue framework is made up of proteins, so a diet poorly made up of this macronutrient also has this harmful potential. Deficiency of micronutrients such as vitamins A, C and D and calcium are well known to be risk factors for enamel hypoplasia in preterm [28]. Low birth weight has been linked to a risk of developing enamel defects. Apart from Ghanim et al. [29], who found higher odds of enamel defect with low birth weight after adjusting for confounding, there was little evidence of an association between enamel defect and low birthweight.

## Conclusion

The mechanisms that link pathophysiological disorders with enamel hypoplasia are varied. Individuals with enamel defects experienced high stress levels during pregnancy or early childhood. Between the fourth and the fifth month of gestation, a window for the occurrence of disorders in the protein matrix and in the calcification of dental enamel in both dentitions can be checked since it is at that moment that the formation of the dental crown begins. However, the etiology of enamel defects is still unclear, but there is a strong indication that adverse events may influence this tissue's complex formation during pregnancy. The adverse events resulting from COVID-19 can be considered a risk for enamel defect as already mentioned. However, studies need to be directed to elucidate this relationship.

## Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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## Conflict of Interest

The authors declare no conflicts of interest.

## Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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