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Getting ahead of the oral health game: it starts before we're born?

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Abstract

Dental caries is one of the most common chronic diseases affecting individuals of all ages. Caries in the primary dentition is one of the main risk factors for caries in the permanent dentition. Preventing the development of the first carious lesion is fundamental not only to long term health and wellbeing but to reducing the burden of this disease on individuals, families and the community. Described as the developmental origins of health and disease, events from the prenatal period are increasingly recognised as having a significant impact on later health outcomes. While social and behavioural factors from this period have long been linked with oral health, emerging evidence of the influence of epigenetics and early life programming of microbiome and host response suggests that the prenatal period provides a timely opportunity for preventive interventions. Pregnancy is an ideal time to focus on health promoting activities as most women have regular interaction with health care professionals who can target risk factors before the onset of disease. This paper summarizes contemporary understanding of the role of pre- and perinatal factors on child oral health and describes how this evidence might be used by all health professionals to ensure infants start life ahead in the oral health game.

Introduction

The first years of life, starting from conception, are recognised as the key period for the determination of future susceptibility to a broad range of illnesses.¹ The sensitivity of the developing foetus to the maternal environment is not an entirely new concept, as demonstrated by the well-established impact of smoking on adverse pregnancy outcomes.² However, rapid developments in understanding the developmental origins of health and disease (DoHAD) have extended the implications from this period to well beyond early life, with compelling evidence to suggest a key role in the onset of common non-communicable diseases, such as dental caries, that were thought to occur later in childhood and even adulthood. Despite emerging evidence, clinical dental practice has been slow to espouse the philosophy. This review draws on the considerable evidence for prenatal and early life programming of dental caries risk to discuss the subsequent clinical implications for dental practitioners involved in the care of families and young children.

From mother to child – how do factors from pregnancy and birth influence future dental health?

Central to the DoHAD concept is the complex interplay between environmental factors and biological pathways, resulting in 'biological embedding' or programming of future disease.³ Early life is a time of intense development, marked by a never again repeated phase of rapid adaptability in the developing foetus/child.⁴ Environmental cues during this period, from nutrition to attachment with caregivers guide this development. However, while this adaptability ensures versatility at the time, some adverse external stimuli may also lead to poor long-term health outcomes.¹

Developmental defects of enamel (DDE), including Hypomineralised Second Primary Molars and Molar Incisor Hypomineralisation, arise as a result of events in pregnancy and early life and have been shown to be major risk factors for dental caries. Frequently, the increased caries risk associated with early life, are attributed to DDE, with weakened enamel considered to be more susceptible to carious lesion formation. However, this association is often not tested, nor quantified and other mechanisms could also be involved in early life programming of future caries risk. For example, human microbiome could be an alternate pathway by which such risk is mediated. The human body has as many bacteria as it does human cells.⁵ In most cases, these microbial populations exist in a symbiotic, or mutually beneficial relationship, with the host.⁶ A number of factors in early life, including the use of broad-spectrum antibiotic therapy or, as in the case of dental caries, frequent intake of fermentable carbohydrates, could lead to dysbiosis early in life.⁷ Additionally, by impacting on family and child stress, health literacy and access to care, social and economic disadvantage tends to cumulate from pregnancy, increasing future disease susceptibility.⁸ This cumulative effect, possibly due to links between poverty and a range of factors that influence child development, including alcohol and tobacco use, nutrition, stress, violence and obesity, begins from conception. Emerging DNA-based technologies are rapidly changing the understanding of how early environment can influence later disease. Epigenetics, through molecules that interact with the gene sequence (or DNA) to modify gene expression, are an increasingly recognised biological process through which early life events may influence the disease risk of the developing foetus.¹ Although few studies have investigated the connection, epigenetic changes may lead to increased risk of dental caries by modulating expression of genes involved in enamel formation, taste, immunity and saliva, possibly as a response to unfavourable events in pregnancy and early life.⁹ Understanding the underlying mechanisms linking early life events to later formation of carious lesions through coordinated clinical and laboratory based approaches will be a key to eventually developing targeted, individualised preventive strategies.

Vitamin D

Vitamin D synthesis occurs in the skin as a result of exposure to sunlight (ultraviolet B).¹⁰ In addition, vitamin D may be ingested through a limited number of foods, including certain fish, eggs and fortified margarine and dairy products, or taken as supplements. Lack of vitamin D can lead to reduced levels of calcium and phosphate, which in turn leads to abnormal mineralisation of calcified structures including the dental hard tissues and in particular enamel.¹¹ (Figure 1) In addition to affecting the availability of calcium and phosphate, vitamin D has a range of functions in other tissues, including in immune modulation that raises the potential of an alternative mechanism for increasing caries risk.¹²

Although vitamin D clearly plays a role in the biological process of tooth formation and immunity, understanding the relationship with dental caries, and the potential benefit of supplementation, is challenging and gives rise to a number of questions including, is vitamin D deficiency a cause of dental caries? If so, what is the dose-response nature of this relationship and by which mechanism (DDE or host immunity or both?) And is the timing of deficiency relevant? Additionally, is vitamin D supplementation likely to reduce caries risk, and if so, at which dose and is timing of supplementation relevant? At present, even though dental caries has been linked with vitamin D in two robust reviews^{13,14}, there is a lack of clear consensus regarding the benefit of supplementation.

A systematic review and meta-analysis of 24 randomised clinical trials (RCTs) found a 47% reduction in caries-risk following dietary vitamin D supplementation or UV radiation.¹⁵ The review combined studies on participants of all ages, with all forms of supplementation and therefore, beyond indicating that supplementation is beneficial, does not answer important questions regarding dosage and timing. Additionally, the authors acknowledge a reasonable risk of bias in 22 of studies, all of which had been conducted more than 60 years earlier. The evidence from recent observational and interventional studies is conflicting, with some studies showing higher caries in children with lower vitamin D levels^{16,17} and others finding no such association^{18,19}. The clinical relevance of such cross-sectional studies may be limited. If DDE are the main reason for the higher caries rates, the critical period would be during pregnancy or early life when tooth formation is most active. While some observational studies have reported lower caries rates in children with supplementation early in life or in pregnancy^{20,21}, adherence to supplementation and subsequent vitamin D levels are influenced by racial and socioeconomic factors, and therefore, despite attempts by investigators to adjust for such factors, such outcomes must be interpreted with caution.^{22,23} Further RCTs of the effectiveness of vitamin D supplementation in reducing the prevalence of dental caries are needed.

Determining the ideal serum vitamin D level has been complicated by the seasonal variation in serum vitamin D, imprecision in laboratory measurements and limitations of observational studies to

identify appropriate dose-response relationships.²⁴ Given the links between vitamin D deficiency and DDE and dental caries, dental practitioners need to be cognisant of the current guidelines regarding vitamin D deficiency and supplementation. Vitamin D levels of 50nmol/L and above are considered healthy for infants, children, adolescents and adults, including during pregnancy.^{25,26} Vitamin D levels at 30-49 nmol/L are considered mildly deficient, 12.5-29 moderately deficient and less than 12.5nmol/L severely deficient. Vitamin D screening and management of deficiency is risk-based (Box 1) and may include increased exposure to sunlight or supplementation, with either daily oral supplements or high dose intermittent supplementation. Due to the significant systemic influence of vitamin D, screening and supplementation should be performed in consultation with a medical practitioner.

BOX 1 (adapted from ²⁶)

Risk factors for low vitamin D

- Lack of skin exposure to sunlight (due to lifestyle factors, chronic illness or hospitalisation, complex disability, covering clothing)
- Dark skin
- Medical conditions or medications affecting vitamin D metabolism and storage (obesity, end-stage liver disease, renal disease, drugs that increase vitamin D degradation such as rifampicin and anticonvulsants, or fat malabsorption [eg, in cystic fibrosis, coeliac disease and inflammatory bowel disease])
- Exclusively breastfed infants of mothers with vitamin D deficiency and at least one other risk factor.

Maternal smoking in pregnancy

Oral health professionals play an important role in smoking cessation, particularly given the impact of smoking in oral cancer and periodontal disease.^{27,28} There is emerging evidence to suggest that smoking cessation may also be important in reducing caries susceptibility. A systematic review found that seven out of eight observational studies reported a positive association between prenatal maternal smoking and early childhood caries in children.²⁹

Although still speculative, prenatal smoking may lead to developmental dental defects by interfering with tooth mineralisation in utero, or by affecting the microbiome of the child, either directly, or by altering the development of immune pathways in the foetus.³⁰ An animal study found hard tissue aberrations in mandibular molars of rat foetuses after maternal exposure to second hand smoke, including delayed development and reduced thickness, volume, density and hardness of enamel.³¹ The authors suggested that nicotine may interfere with ameloblast proliferation and differentiation or reduce blood supply to the developing tooth.

Using observational studies to evaluate the effects of smoking is difficult, because of the role of common socio-economic, dietary and behavioural risk factors that may confound and exaggerate the actual association. Nevertheless, most studies adjust for the influence of these factors using statistical methods, and may provide the only ethical way of clinically evaluating this relationship. Another limitation of the existing evidence is the lack of clarity regarding the importance of dose (number of cigarettes) and timing (stage of pregnancy) on the relationship between prenatal smoking and caries. A Japanese study of 6412 3-year-old children found that the 1st trimester of pregnancy is a critical time, with a much stronger association with dental caries in the offspring than at other stages.³² A retrospective study of 2395 Italian children aged 24-30 months found that smoking more than 5 cigarettes a day in pregnancy led to a higher caries risk in the offspring.³³ Smoking in studies is usually based on self-report, which has been shown to be accurate, despite the potential for under-reporting.³⁴

Although further studies are needed to explore the relationship between smoking and dental caries, given the clear oral and general benefits of smoking cessation, particularly in pregnancy, support from oral health practitioners is highly recommended.

Maternal obesity

Two cohort studies from Scandinavia reported obesity during pregnancy was associated with higher caries rates in the children.^{35,36} As both studies adjusted for several confounders including socio-economic status and smoking, the authors suggested that these observations may be due to either biological influences on the developing foetus, or transfer of dietary habits.

Maternal obesity has been reported to be associated with higher risks of childhood obesity. Although shared dietary and lifestyle preferences may be a major factor in this association, epigenetics may also lead to 'foetal programming' due to influences in the intra-uterine

environment.³⁷ The links between obesity and dental caries are controversial, despite a number of studies showing an association.³⁸

Low birth weight and prematurity

Low birth weight and prematurity are associated with a number of co-morbidities and predisposes individuals to long-term adverse health outcomes.^{39,40} Low birth weight is defined as birth weight of less than 2500g.⁴¹ Further sub-categories within this definition include very low birth weight (less than 1500g) and extremely low birth weight (less than 1000g). In Australia, the rates of low birth weight have remained relatively stable over the last decade, at approximately 6% of all live births.⁴² Prematurity broadly refers to gestational age of less than 37 weeks.

A systematic review of four studies concluded that although there was no evidence of an association between dental caries and low birth weight, a potential association could not be discounted because of the lack of good quality evidence.⁴³

Evaluating the association between low birth weight and dental caries is challenging because low birth weight is an indicator of overall social disadvantage, itself a strong predictor of dental caries.⁴³ Biological links through developmental defects of enamel (i.e hypomineralised teeth), which are strongly associated with low birth weight and prematurity are plausible explanations for an association with dental caries.^{44,45} However confounding this is the fact that low birth weight children enrolled in longitudinal cohort studies are likely to have better access to dental care, and may therefore be at reduced risk of dental caries. Children who are part of such longitudinal studies have regular dental reviews and referral for appropriate services when needed, and therefore may not be representative of population norms.⁴⁵

Low birth weight may be due to prematurity (less than 37 weeks of gestation) or intra-uterine growth restriction (IUGR).⁴⁶ As these have different risk factors and effects on the child, their effects on dental caries may also be different. A recent study evaluating prematurity as well as two different measures IUGR revealed associations in opposite directions.⁴⁷ Whereas pre-term birth was associated with higher levels of dental caries, IUGR was found to be protective. The authors explain these findings by citing changes in oral bacterial due to eruption delay and increased use of antibiotics amongst children with IUGR. However, the latter is controversial, as maternal/infant? antibiotic use is also reported to be associated with early childhood caries.⁴⁸

Mode of delivery

Delivery mode appears to affect various facets of the human microbiome and as such, has led to suggestions that it may also influence caries experience.⁴⁹ A Danish cross-sectional study reported

that children who were delivered vaginally were more likely to foster healthy bacteria in saliva.⁵⁰ A prospective study found caesarean delivery was associated with earlier colonisation by *S. mutans*, and reduced diversity in bacterial strains.⁵¹ Given the important role played by oral bacteria in dental caries, the mechanisms for these associations need further investigation. However, speculation about the impact of such factors on microbiome is often simplistic tending to return to the now discounted theories of dental caries being an infectious disease. Indeed, the two studies evaluating the association between mode of delivery with clinical dental carious lesions contradicted the above. In one, cross-sectional Thai study 3-5 year old children were shown to have higher levels of dental caries and *S. mutans* if born vaginally while in a Danish study, no association was found between dental caries and delivery mode.^{52,53} Further studies investigating the impact of mode of delivery on the oral microbiome may clarify the process leading to dysbiosis that results in carious lesions, but at present there is insufficient evidence for a direct association.

Access to oral health education and professional dental services during pregnancy

Pregnant women are often unaware of the role of events in pregnancy on the later oral health of their children or the importance of oral health during pregnancy. Poor oral health, particularly periodontal diseases are associated with increased risk of adverse pregnancy outcomes such as pre-eclampsia, prematurity and low birth weight.^{54,55} Unfortunately, despite pregnancy generally being a time of increased contact with health professionals, professional dental care is frequently lacking.⁵⁶⁻⁵⁸ The barriers to care include a lack of affordability and time and concerns about safety of dental treatment in pregnancy. Oral health professionals may also be hesitant to provide care in pregnancy.⁵⁹ Lack of affordability of dental services during pregnancy increases the risk of poor oral health in the mother and child and is an apt example of the cumulative impact of socioeconomic status and poverty on later oral health. Improving utilisation of professional dental care may be possible through prioritisation of pregnant women in public sector waiting lists and education of oral health professionals and the public about the importance and safety of dental care in pregnancy.⁵⁷ In addition, integration of oral health education and promotion through existing and widely utilised antenatal services, such as obstetricians and gynaecologists and midwives may enable broader dissemination of important oral health messages as well and referral to appropriate professional services.⁶⁰

Conclusions

The role of events from pregnancy and birth on later caries risk is an emerging field of research and, as demonstrated in this review, further epidemiological, clinical and laboratory studies are needed to clarify the nature of these relationships. Nevertheless, some factors, such as vitamin D levels and

maternal smoking appear to be better supported than others, such as birth weight and mode of delivery. Oral health practitioners serve as a valuable and respected source of information for the general public and can be instrumental in evidence-based health promotion, particularly in pregnancy.

While early programming of future disease may appear to be somewhat deterministic, appearing to negate the influence of later preventive measures, shifting the focus to pregnancy and birth also provides exciting potential for early intervention. The concept of DoHAD requires a change in the approach to prevention, prioritising interventions long before disease onset. Given the shared risk factors between dental caries and other NCDs, integrating oral health as a key component (both outcome and determinant) will help to break down the traditional barriers that segregates oral health from overall health and development. Further as costs for management of NCDs rapidly spiral beyond sustainable levels, intervention in pregnancy, such as smoking cessation programmes, or vitamin D supplementation where appropriate, well before biological and cumulative processes have programmed the developing foetus for future risk is likely to yield much more benefit in terms of prevention. Finally, pregnancy is a time of increased interaction with health services and targeted, evidence-based, cost-effective oral health promotion may be more feasible to provide at this time.

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Figure Legend

Figure 1: The lower primary dentition of a child affected by developmental defects of enamel due to vitamin D deficiency in pregnancy and infancy. Note the generalized white opacities affecting the primary molars in particular.

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