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Enamel defects in prematurely born, low birth-weight infants

Janice F.L. Pimlott, RDH, BScD, MSc Thomas P. Howley, PhD
Gordon Nikiforuk, DDS, MSc, FRCD Pamela M. Fitzhardinge, MD, FRCP(C)

Abstract

The purpose of this study was to relate the influence of birth and metabolic parameters of the low birth-weight neonate to the development of the primary teeth. The role of hypocalcemia as a specific determinant of enamel hypoplasia was examined. A total of 106 low birth-weight children ranging in age from 18 months to 8 years were examined to determine the frequency of enamel defects.

Enamel hypoplasia was found in primary maxillary incisors in 38% of the sample; enamel hypocalcification on maxillary permanent incisors affected 58% of the sample. The relationship between enamel hypoplasia and plasma calcium was not statistically significant; several mitigating factors are discussed. However, those neonates with low calcium readings had significantly lower birth weights, shorter birth lengths, lower gestational ages, lower 1-min Apgar scores, lower admission temperature, and longer time to regain birth weight than those with no low calcium readings.

The high prevalence of enamel hypocalcification in the permanent teeth was speculated to be the result of metabolic stresses during the first few months postterm. This study showed no correlation between enamel hypocalcification and the birth parameters.

Premature births (gestation age less than 37 weeks) account for 7-10% of all live births. Prematurely born children are subject to a variety of metabolic stresses and therefore provide an opportunity for studying the effect of severe metabolic parameters on both development and the eruption of teeth. In this paper the prevalence of enamel hypoplasia and hypocalcification and possible etiologic factors are considered.

While the specific biochemical cause of enamel hypoplasia has not been determined, there has been growing evidence in recent years that enamel hypoplasia is linked to calcium homeostasis. This hypothesis is based on reports of a high prevalence of enamel hypoplasia in children who have pediatric disturbances such as neonatal tetany, vitamin D-dependent rickets (VDDR), simple rickets, renal disease, and cerebral palsy, and also in infants of diabetic mothers.[1-8] The prevalence of enamel hypoplasia in the prematurely born has been reported at between 18 and 43%.[9,10] The metabolic factor common to all these conditions is episodes of hypocalcemia.

Several studies suggest a direct relationship between enamel hypoplasia in primary teeth and neonatal hypocalcemia. Stimmler et al.[11] studied 12 children who had severe late neonatal hypocalcemia with convulsions during the fifth to tenth day of life. All had brown bands of hypoplastic lesions on the primary canines and molars. In most cases the primary central and lateral teeth were not affected; this was attributed to crown completion before the onset of the hypocalcemia. They reported that the observed abnormalities were not characteristic of those found in the prematurely born children as reported by Miller and Forrester[3] or Sarnat and Schour.[12,13] However, in children with hypocalcemia associated with congenital hypoparathyroidism, the enamel hypoplasia had characteristics similar to lesions observed in prematurely born infants. Purvis et al.[14] histologically examined primary teeth with similar enamel hypoplastic defects and suggested that the condition might have been produced by a vitamin D deficiency during pregnancy and further aggravated by reduced exposure to sunlight during winter months, thereby producing secondary hyperparathyroidism in the mother. This was challenged by Stimmler et al.[15] who maintained that the enamel defects were caused postnatally rather than prenatally.

Table 1. Prevalence of Enamel Hypoplasia and Hypocalcification in Low Birth-weight, Prematurely Born Children

A. **Enamel Hypoplasia**

Arch	*Teeth*	*Tooth Numbers*	*Number of Children*	*% Prevalence Incisal Half*	*Gingival Half*	*Either Half*
Maxillary	Medial incisors	51, 61	72	35[1]	5[2]	36
	Lateral incisors	52, 62	87	33	3	34
	Any incisors	51, 52, 61, 62	87	37	3	38
	Canines	53, 63	101	8	0	8
	1st molars	54, 64	103	3	1	3
	2nd molars	55, 65	82	2	0	2
	Any posterior	53, 54, 55, 63, 64, 65	104	11	1	11
Mandibular	Medial incisors	71, 81	48	4	0	4
	Lateral incisors	72, 82	70	3	0	3
	Any incisors	71, 72, 81, 82	71	4	0	4
	Canines	73, 83	98	2	1	3
	1st molars	74, 84	104	3	2	3
	2nd molars	75, 85	82	4	0	4
	Any posterior	73, 74, 75, 83, 84, 85	105	6	3	8
Either arch any tooth			106	-	-	37

B. **Enamel hypocalcification**

			Premature Sample		Normal Sample	
Arch	*Teeth*	*Tooth Numbers*	Number of Children	% Prevalence	Number of Children	% Prevalence
Maxillary	Medial incisors	11, 21	37	59	40	8
	Lateral incisors	12, 22	17	12	—	—

[1] This percentage is based on 71 children instead of 72, as the medial incisors of 1 child were so worn that the incisal half could not be assessed.

[2] This percentage is based on 66 children instead of 72, as the medial incisors of 6 children were erupted only partially and the gingival half was not visible.

Levine and Keen[16] examined histologically and microradiographically 25 primary teeth of children with neonatal hypocalcemia. They found no evidence to suggest that the defect was caused prenatally as Purvis et al.[14] had indicated. However, they found that the appearance of the hypoplastic lesion was similar to those reported in two other conditions: kernicterus[3] and cerebral palsy.[17,18]

Noren et al.[7] found an increased prevalence of enamel hypoplasia in infants of diabetic mothers. They speculated that these enamel defects were due to functional hypoparathyroidism which resulted in states of hypocalcemia and hyperphosphatemia.

In a definitive study of children with chronic disorders of calcium and phosphorus homeostasis, Nikiforuk and Fraser[8] found enamel hypoplasia in those conditions where hypocalcemia existed (e.g., hereditary VDDR and hypoparathyroidism), but not in those conditions with hypophosphatemia and normal calcium levels (x-linked hypophosphatemic rickets). Therefore, they concluded that enamel hypoplasia was not related to plasma phosphorus levels, but rather to hypocalcemia during the development of the teeth.

The purpose of the present study was to relate the influence of birth and metabolic parameters (especially hypocalcemia) in prematurely born, low birthweight neonates on the development of their primary teeth.

Methods and Patient Sample

In this study all children were born prematurely (gestational age < 37 weeks) and had birth weights < 1500 g. All were enrolled in the prenatal follow-up program at the Hospital for Sick Children in Toronto. A total of 106 children (57 males, 49 females) ranging in age from 18 months to 8 years were studied by a single examiner to determine the frequency of enamel defects, specifically enamel hypoplasia and enamel hypocalcification. Enamel hypoplasia was defined as a quantitative defect in the enamel surface, while enamel hypocalcification was defined as the presence

Table 2. *t*-Tests of Differences in Birth Variables Between Enamel Hypoplasia Groups and Between Lowest Serum Calcium Groups

Birth Variable		*Enamel Hypoplasia*		*Lowest Serum Calcium*	
		YES	NO	<6 mg/100 ml	≥6 mg/100 ml
Birth Weight (g)	Mean	1119	1128	1027	1167
	SD	233	217	199	212
	n	33	54	32	71
	p	.85		.002	
Birth Length (cm)	Mean	35.83	37.54	35.65	37.40
	SD	4.28	2.37	3.43	2.85
	n	32	53	31	69
	p	.04*		.009	
Birth Head Circumf. (cm)	Mean	27.55	26.25	26.57	26.61
	SD	5.24	2.10	3.90	3.22
	n	32	53	31	69
	p	.19*		.95	
Gestational Age: Clinical (weeks)	Mean	29.97	30.02	28.94	30.38
	SD	2.14	2.81	1.98	2.62
	n	31	51	31	66
	p	.93		.008	
Apgar Score: 1 min	Mean	4.69	4.40	3.52	4.82
	SD	2.39	2.51	1.96	2.60
	n	29	48	25	60
	p	.61		.03	
Apgar Score: 5 min	Mean	6.44	6.70	6.21	6.57
	SD	2.85	2.48	2.89	2.45
	n	27	46	24	56
	p	.69		.56	
Admission Temp. (°C)	Mean	36.18	35.86	35.45	36.10
	SD	1.19	1.11	1.06	1.12
	n	32	52	30	69
	p	.24		.008	
Days to Regain Birth Weight	Mean	19.43	21.64	25.15	19.85
	SD	8.53	11.43	10.39	9.71
	n	30	48	26	65
	p	.36		.02	

* *T*-test for unequal variances.

of an area of enamel exhibiting a distinct white opalescence with no detectable structural defect. In addition, a control sample of 40 full-term children was examined for the presence of enamel hypocalcification. The children resided in an area where the water supply contained 1 ppm fluoride; no subject reported receiving fluoride supplements.

Data regarding birth parameters for each child were gathered. These included: birth weight; birth length; birth head circumference; gestational age; Apgar scores; pH at birth; temperature at birth; time to regain birth weight; and the presence of absence of asphyxia, apnea, and convulsions at birth. Plasma calcium readings during the first week of life also were obtained, as well as data pertaining to the growth of these children up to the age of 2 years.

Results

Enamel Hypoplasia

Table 1a shows the prevalence of enamel hypoplasia in this sample of 106 prematurely born children.

Thirty-seven per cent of the children had at least 1 enamel hypoplastic defect (Fig 1). The overwhelming majority of these defects were noticed on the primary maxillary incisors, and most of the defects were located on the incisal half of the tooth. Thirty-eight per cent of the 87 children with maxillary incisors had these defects; only 11% of the 104 children with posterior (canine, first, and second molars) maxillary teeth had defects. The prevalence of enamel hypoplasia in mandibular teeth was much lower (4-7%).

Enamel Hypocalcification

An unanticipated finding of this study was the presence of enamel hypocalcification in the incisal quarter of the permanent maxillary incisors, and to a lesser degree in the mandibular incisors (Fig 2). These hypocalcified lesions appeared as opaque white flecks or streaking not unlike those observed in mild fluorosis. Table 1b shows that the prevalence of enamel hypocalcification in the 37 children in the premature group who did have at least 1 permanent maxillary central incisor was 59%. A substantially smaller prevalence (12%) was found in maxillary lateral incisors. The authors also were able to obtain an estimate of the prevalence of enamel hypocalcification in normal children. In a sample of 40 full-term, normal birthweight children, only 3 (7.5%) displayed hypocalcification on either of these medial incisors. This difference in proportions is highly significant ($p < .001$).

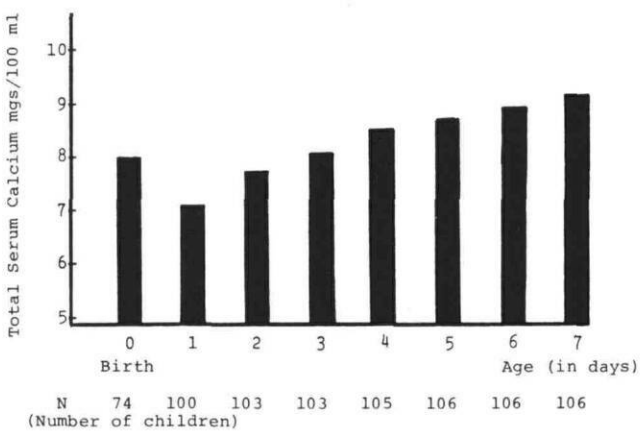

FIG 1. Mean daily total serum calcium values for the first week postnatally.

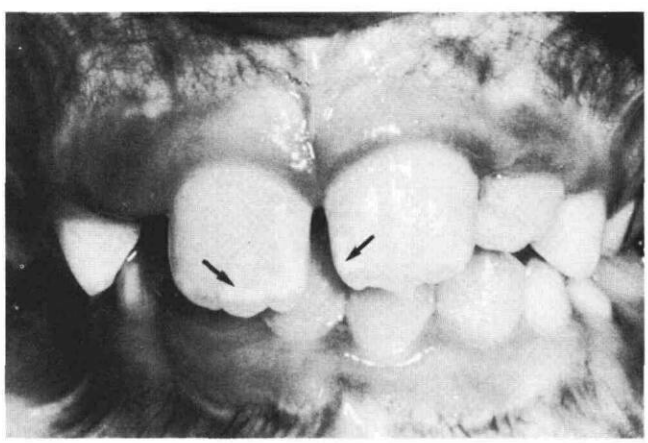

FIG 2. Enamel hypocalcification of permanent incisors in a prematurely born, low birth weight child. Arrows indicate opalescent lesion localized to the incisal edge.

Serum Calcium Levels

Serum calcium levels were measured up to 4 times daily during the first week of life. The daily mean of these readings for each neonate was calculated. The means of the daily calcium levels for the entire sample of neonates from birth to the seventh day after birth are shown in Figure 1. From 8.05 mg/100 ml at birth, the mean calcium level dropped to 7.22 on the first day, then increased steadily to 9.30 mg/100 ml on the seventh day after birth.

Previous investigators[19-21] have indicated that a serum calcium reading of less than 6 mg/100 ml is abnormally low. In the present study 32 of the 103 neonates (31%) had at least 1 calcium reading from day 0 to day 3 which was below 6 mg/100 ml.

Relationships Among Enamel Hypoplasia, Serum Calcium, and Birth Variables

No significant differences in daily calcium levels between those with and without enamel hypoplasia on their maxillary incisors were shown in *t*-tests. This also was shown by an insignificant ($p = .32$) chi-square test for association between presence or absence of enamel hypoplasia and of low (< 6 mg/100 ml) calcium readings.

Table 2 shows the relationships of various birth measurements to the presence or absence of enamel hypoplasia and to the presence or absence of low calcium readings. No significant differences were found between the enamel hypoplasia groups. However, those neonates with low calcium readings had significantly lower birth weights ($p = .002$), shorter birth lengths ($p = .009$), lower gestational ages ($p = .008$), lower 1-min Apgar scores ($p = .03$), lower admission temperatures ($p = .008$), and longer time to regain birth weight ($p = .02$) than those with no low calcium readings. The number of days to regain birth weight is an important variable in reflecting the health status of the neonate, since it reflects the severity of the neonatal course. Thus, a low serum reading in the first 3 days after birth is closely related to severe conditions of birth.

Discussion

In this study, 38% of the group had enamel defects in the primary teeth, predominantly in the maxillary

incisor teeth; this is consistent with previous reports.[10,22-24]

Prematurely born infants may be classified on the basis of their rate of intrauterine growth as compared with the growth of full-term infants. Those whose rate of growth at the time of birth is within 2 standard deviations of the mean are considered appropriate for gestational age (AGA). Infants are considered small for gestational age (SGA) if their growth is retarded and their birth weight is more than 2 standard deviations below the mean.[25] Of the 87 children in the study who had maxillary incisors, 26 were classified as SGA. The prevalence of enamel hypoplasia was the same in the AGA and SGA infants. This finding also is in agreement with Funakoshi et al.[23] In addition, these investigators reported a significant increase in enamel hypoplasia in those infants who had a gestational age of < 34 weeks. However, a similar comparison was not possible in this study group, as 96% of the group had a gestational age of < 34 weeks. Instead, the authors compared the prevalence of enamel hypoplasia in those who had a gestational age of ≤ 30 weeks to those > 30 weeks, and found no significant increase in those with the lesser gestational age ($p > .05$).

In this study it was found that the relationship between enamel hypoplasia and plasma calcium was not statistically significant. Further, the prevalence of enamel hypoplasia in children with and without a convulsive period was not significantly different. There were no significant differences between the presence or absence of enamel hypoplasia and birth variables, including birth weight, birth length, birth head circumference, and Apgar scores at 1 and 5 min. However, all these birth variables, except the 5-min Apgar scores, showed significant differences when the infants were grouped according to whether or not they had a calcium reading of < 6 mg/100 ml. The lack of a relationship between enamel hypoplasia and plasma calcium in this study is anomalous in view of the strong evidence of a correlation in the studies involving children with VDDR and neonatal tetany.

There are several possible explanations why, in this study, plasma calcium concentrations and enamel hypoplasia were not significantly related. First, all neonates in the study received IV transfusions of calcium gluconate as soon as a hypocalcemic state was detected. Even though the treatment did not correct the hypocalcemia entirely (low total plasma calcium levels frequently were detected), nevertheless the procedure may have masked the intrinsic hypocalcemia sufficiently and altered its effects on the formation of enamel. Second, it may have been desirable to obtain plasma calcium values for longer periods than 1 week; however, these were not available. The duration of hypocalcemia may be especially significant, since it is known that all children with VDD exhibit enamel hypoplasia and all have hypocalcemia for extended periods of time unless treated. Third, only the total plasma calcium was measured at the time the neonates were admitted to the hospital (1975-76); ionic calcium was not analyzed. Radde et al.[26] reported that total calcium determinations reflected calcium ion levels with only 80% accuracy when a correlation coefficient between total and ionized calcium was determined. This is particularly significant in the neonate since treatment of acidosis rapidly may deplete ionized calcium. Fourth, it is best to evaluate enamel hypoplasia in primary teeth at an earlier age than 6 years since wear to the central incisors can be severe, thus abrading the incisal portion which is the area usually affected by neonatal factors. Watson[18] also found abrasion to affect his sampling accuracy. Finally, other factors not considered in this study which may have affected plasma calcium concentrations are: the prolonged periods of incubation of some children, the use of different feeding regimens (breast, formula, and intravenous) and, most importantly, the use of vitamin D supplements given at 2 weeks of age.

The possibility that enamel hypoplasia is caused by factors other than low calcium cannot be dismissed entirely in spite of its close association with pediatric conditions where hypocalcemia is relatively common. However, the mitigating factors discussed above, when considered as a whole, may have contributed to the equivocal results and prevented a definitive testing of the hypothesis that enamel hypoplasia and plasma calcium are related.

Apart from the description of enamel opacities associated with excessive systemic ingestion of fluoride, there are no previous reports in the literature relating to a high prevalence of hypocalcification in the permanent teeth of any group of children.

In prematurely born, low birth-weight children, the enamel opacities, while common, were relatively mild and were limited to the incisal edges of central incisors and the occlusal tips of the first permanent molars. Evidence also is presented (Table 1) that the lateral incisors are affected, but other teeth could not be investigated due to the age of the children studied. Chronological tables of enamel development indicate that the incisal portion of the central incisors and occlusal tip of the first permanent molar develop during the neonatal and early infancy period. The metabolic stresses present during the first few months postterm that might account for the disruption of the development of the enamel in such a way that opalescent zones formed remain to be delineated.

The authors have been unable to show a relationship between enamel hypocalcification and any birth parameter such as birth weight, gestational age, or

Apgar scores. Growth rates and hypocalcemia also are not related to the development of the hypocalcified areas. Thus, the unraveling of specific metabolic factors that may relate to the formation of an opalescent area will have to await more definitive epidemiological studies. Since this is the first report of a high prevalence of these lesions, it would be important to characterize it further by studying other cohort groups.

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Professor Pimlott is an assistant professor, Division of Dental Hygiene, Faculty of Dentistry, University of Alberta, Edmonton, Alberta, T6G 2N8. Dr. Howley is an assistant professor, biometrics, and Dr. Nikiforuk is a professor, preventive dentistry, University of Toronto. Dr. Fitzhardinge is chief, pediatrics, Mt. Sinai Hospital, Toronto. Reprint requests should be sent to Dr. Pimlott.

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