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Effect of umbilical cord essential and toxic elements, thyroid levels, and Vitamin D on childhood development☆

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Abstract

Introduction: The in-utero environment has dramatic effects on childhood development. We hypothesized prenatal levels of inorganic agents, thyroid levels, and Vitamin D effect childhood development.

Methods: Umbilical cord blood was collected from April 3, 2013 to January 30, 2014 and analyzed for 20 different elements, thyroid and Vitamin D. A retrospective review (n = 60) was performed of well-child examinations from birth to 5 years old (y.o.).

Results: There were associations with calcium and 4 month BMI (p = <0.01), 12 month language (p = 0.03); Magnesium and 6 month language (p = 0.04) and gross motor skills at 5 years old (y.o.) (p = 0.03); Copper and 12 month fine motor (p = 0.02); Zinc with fine motor (p = <0.01) and language (p = 0.03) at 2 y.o.; Manganese was associated with language development at 2 y.o. (p = 0.02); Molybdenum and fine motor at 12 months of age (p = 0.02); Selenium with gross motor (p = 0.04) and BMI (p = 0.02) at 5 y.o.; Lead with cognitive function at 4 months (p = 0.04) and 2 y.o. (p = 0.01); Mercury with gross motor at 4 months (p = 0.04) and language at 2 y.o. (p = 0.02). Platinum at 12 months of age (p = <.01) as well as multiple associations at 5 y.o.

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CRediT authorship contribution statement

Jesse Cottrell, Monica Valentovic: Were involved with conceptualization, Experimental design, Methodology, Sample preparation, Data analysis and manuscript preparation. **Chelsea Nelson, Cahterine Waldron, Mackenzie Bergeron, Abigail Samson:** Were responsible for Data collection and Data analysis.

Exclusive Submission Statement

The following manuscript, Effect of umbilical cord essential and toxic elements, thyroid levels, and Vitamin D on childhood development, is being exclusively submitted to *Biomedicine and Pharmacotherapy*.

Disclaimers

The views expressed in this submitted article are strictly the view of the authors and not an official position of the institution or funder.

Declaration of Interest

The authors do not have any conflicts of interest. The authors have no financial conflicts to disclose regarding this study.

(p = <.01). Thyroid function tests for free T3 were associated with multiple cognitive and physical milestones. T3 Uptake was associated with 5 y.o. gross motor skills (p = 0.02). Total and Free T4 was associated with cognitive development (p = <.01) and fine motor development, respectively. Vitamin D was associated with a delay of fine motor development (p≤,0.01).

Conclusion: There were multiple associations between umbilical cord essential and toxic elements, thyroid levels, and Vitamin D on childhood development.

Keywords

Metals; Child development; Umbilical cord; Thyroid; Vitamin D

1. Introduction

The intrauterine environment is the epicenter where embryonic and fetal development either prospers or flounders. This in-utero milieu is influenced by environmental factors including nutrition, stress, toxicants, hormones, and essential elements. These factors have been shown to have dramatic effects long after birth on childhood development [10–12,4,7].

The developing fetus is susceptible to environmental insults as cells are rapidly dividing. Organogenesis begins as early as 3 weeks post-conception and is usually complete by about 8 weeks gestation, creating the optimal environment for teratogenic substances to cause damage to the developing embryo. These organ systems continue to develop and differentiate until birth. The brain is unique in that the different parts are responsible for different functional domains. These domains develop at different times (i.e., motor control, sensory, intelligence, and attention). Additionally, the cell types of the nervous system have different windows of vulnerability with varying sensitivities to environmental agents [11]. The brain undergoes periods of rapid growth and development in mid and late pregnancy making it vulnerable to changes in the intrauterine environment [4].

While studies have examined the effects of essential metals and toxic elements on birth outcomes and neonatal characteristics, studies assessing exposure and childhood developmental milestones are limited. We hypothesized that umbilical cord essential and toxic elements, thyroid levels, and Vitamin D affect childhood development.

2. Methods

From April 3, 2013 to January 30, 2014 umbilical cord blood was collected and analyzed at delivery for 20 essential and toxic metals (calcium, magnesium, copper, zinc, manganese, lithium, selenium, strontium, molybdenum, arsenic, barium, cadmium, cobalt, lead, mercury, nickel, platinum, silver, thallium, uranium), vitamin D, total T3, T3 uptake, T4, free T4, and Thyroid Stimulating Hormone (TSH). All deliveries took place at Cabell Huntington Hospital in Huntington, WV. The mothers were residents of Ohio, Kentucky, or West Virginia.

The 20 inorganic elements were measured by The Great Plains Laboratory, Inc. located in Lenexa, KS. According to the lab protocol, The Great Plains Laboratory analyzes the elements in whole blood by inductively coupled plasma mass spectroscopy following specimen digestion with nitric acid in a closed containing microwave oven system. The procedure measures the total concentration of an element in whole blood, regardless of biochemical form and regardless of partitioning of the element in blood fractions. The levels of vitamin D, total T3, free T3, T3 uptake, total T4, free T4, and TSH were measured according to lab protocol at Cabell Huntington Hospital. Inclusion criteria were those who had successfully delivered, cord blood was obtained, and follow-up well-child examinations were available in the electronic medical record. Exclusion criteria was non-collection of cord blood, inadequate collection, or no pediatric follow-up available for review.

A retrospective review was performed of well-child examinations from 4 months to 5 years old, and 60 patients met inclusion criteria. There were 4 developmental domains assessed; gross motor, fine motor, cognitive, and language. Other parameters included body mass index (BMI) and heart rate, and the Modified Checklist for Autism in Toddlers (M-CHAT) score. Demographic information was extracted from each patient's electronic medical record.

Comparisons and p-values were by one way ANOVA and Chi-square test of independence. The study was approved by the Institutional Review Board at Marshall University (IRB #1679896–3). The project was supported by the Robert C. Byrd Center for Rural Health, Marshall University. Funding was obtained through the Rural Health Initiative grant from the West Virginia Higher Education Policy Commission and the Marshall University School of Medicine Translational Research Pilot Grant program and NIH grant P20GM103434.

3. Results

Maternal demographic information (Table 1) demonstrated a mean age of 26.16 ± 5.01 years and a body mass index of 30.58 ± 6.52. There was a higher proportion of those from urban environments (70%), and 30% of patients admitted to daily tobacco use. Surprisingly, 16 of the 60 patients (27%) did not take a prenatal vitamin during their pregnancy.

Regarding fetal demographics (Table 2), delivery was accomplished at a mean of 38.62 ± 1.90 days with 70% of deliveries occurring vaginally. The length of hospital stay for the neonates was 7.82 ± 15.17 days, which was undoubtedly skewed due to some infants being admitted for extended neonatal intensive care unit stays.

Child development at 4 months of age (Tables 3), 6 months of age (Table 4), 12 months of age (Table 5), 2 years of age (Table 6), and 5 years of age (Table 7) were compared as listed in the accompanying tables.

There was only one difference in the Modified Checklist for Autism in Toddlers (M-CHAT) score for any of the analytes examined, with the free T3 at 18 months of age being associated with 18 passing scores and one failing score ($p = 0.02$).

4. Discussion

The in-utero environment has been shown to have dramatic effects on childhood development [9,12]. Prior studies have shown associations between prenatal exposure to some metals and their effect on cognitive, motor, and intellectual development of the child [10,11,2,4,7,9]. Our study demonstrated that there are multiple associations between umbilical cord essential and toxic elements, thyroid levels, and Vitamin D on childhood development.

In 2015, the International Federation of Gynecology and Obstetrics released an Obstetrics opinion on the reproductive health impacts of exposure to toxic environmental chemicals, stating that "exposure to toxic environmental chemicals during pregnancy and breastfeeding is ubiquitous and is a threat to healthy human reproduction" [3]. For many years there has been widespread concern regarding the teratogenic potential of toxic environmental chemicals and research examining the link with childhood development.

Prior studies have examined the effects of essential metals and toxic elements on neurodevelopmental outcomes. A cohort study in rural Bangladesh determined that in-utero, low levels of cadmium were associated with lower IQ scores at 5 years of age.[2] Elevated cadmium exposure in utero has also been associated with delayed growth patterns in early childhood [2].

Adverse effects mediated by lead and mercury exposure have been more extensively studied. Due to rapid brain development in mid and late pregnancy, lead and mercury appear to have particularly toxic effects [4]. A study assessing the relationship between chromium, lead, cobalt, silver, nickel, cadmium, and mercury presence in amniotic fluid found a negative association with child cognitive function at the age of 2 years [9]. In a cohort of 230, a study by Lin et al. found elevated levels of manganese and lead in utero were associated with delayed cognitive and language development when assessed at the age of 2 [10]. Interestingly, even lower-dose lead exposures have been associated with impairment in intellectual function and attention [11]. In our study we found an association between lead and cognitive function at 4 months of age ($p = 0.0436$) and 2 years of age ($p = 0.0159$), even though lead was not at levels considered toxic for any of the infants in our study. There has also been shown to be evidence between manganese exposure and attention deficit disorder with hyperactivity [13]. In our study manganese was associated with a negative impact on language development at 2 years of age ($p = 0.02$).

Children born with normal thyroid function who experienced thyroid hormone insufficiency in the womb display subtle cognitive impairments [5]. Gilbert et al. differentiated these patterns of cognitive effects as resulting from prenatal versus postnatal thyroid hormone insufficiency [5]. In our study we found numerous associations between various thyroid hormones and developmental outcomes.

Insufficient maternal Vitamin D has been associated increased risk developing maternal conditions such as gestational diabetes and pre-eclampsia.[1] While Vitamin D is known to play a pivotal role in the development of the brain, there is limited and conflicting data on how it effects developmental milestones in a child [6]. Laird et al. examined maternal Vitamin D status and the relationship with childhood neuro-developmental outcomes. Comparing neurocognitive development at age 5, Laird and associates did not observe any clinically significant associations [8]. In a study by Janbek et al., low Vitamin D levels during pregnancy was associated with a negative effect on offspring language and motor development. In our study, Vitamin D was associated with fine motor skills at 2 years of age (p = <.01).

This is the largest study to date examining childhood developmental outcomes for 20 essential and toxic metals (calcium, magnesium, copper, zinc, manganese, lithium, selenium, strontium, molybdenum, arsenic, barium, cadmium, cobalt, lead, mercury, nickel, platinum, silver, thallium, uranium), vitamin D, total T3, T3 uptake, T4, free T4, and Thyroid Stimulating Hormone. As this was a retrospective review, unfortunately only 60 total charts available out of 172 in the original study were available for review. For some of the elements being examined, the levels were below the laboratory cutoff and analysis for these elements in regard to fetal development was not possible.

In our study there are multiple associations between umbilical cord essential and toxic elements, thyroid levels, and Vitamin D on childhood development. Further research is needed to fully understand the reproductive health impacts of in-utero exposure to toxic elements, thyroid levels, and Vitamin D.

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Data availability

Data will be made available on request.

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Table 1

Maternal Information. Calculated mean ± SD (95% Confidence Interval) for continuous variables. N (%) for categorical variables.

	Mean ± SD or n (%)
Age	26.16 ± 5.01
BMI	30.58 ± 6.52
Urban	42 (70.00)
Rural	18 (30.00)
Insurance Type	
None	1 (1.70)
Private	26 (44.07)
Public	32 (54.24)
Mother Length of Hospital Stay	3.58 ± 3.42
Employment Status	
Employed	26 (43.33)
Not Employed	34 (56.67)
Marital Status	
Divorced	4 (6.67)
Married	29 (48.33)
Single	26 (43.33)
Widow	1 (1.67)
Alcohol Use	
Denies	59 (98.33)
Affirms	1 (1.67)
Drug Use	
Denies	53 (88.33)
Affirms	7 (11.67)
Current Tobacco Use (packs per day)	
0.1	1 (1.67)
0.2	3 (5.00)
0.5	8 (13.33)
1	5 (8.33)
3	1 (1.67)
Denies	42 (70.00)
Prenatal Vitamin Use	
No	16 (26.67)
Yes	44 (73.33)

Table 2

Delivery and Fetal Information. Calculated mean ± SD (95% Confidence Interval) for continuous variables. N (%) for categorical variables.

Gestational Age at Delivery (weeks)	**38.62 ± 1.90**
Induction/ Non-induction	
Induction	35 (58.33)
Non- induction	25 (41.67)
Mode of Delivery	
Cesarean	18 (30)
Vaginal	42 (70)
Maternal Hemoglobin	11.81 ± 1.14
Maternal Hematocrit	35.36 ± 4.30
Maternal White Blood Cell Count	12.10 ± 3.78
Maternal Platelet Count	199.87 ± 60.69
Fetal Gender	
Female	27 (45)
Male	33 (55)
Fetal Apgar 1 min	8.47 ± 0.70
Fetal Apgar 5 min	8.97 ± 0.18
Fetal Birth Weight	3.36 ± 0.65
Fetal Head Circumference	34.24 ± 2.18
Fetal Length of Hospital Stay (days)	7.82 ± 15.17
Fetal Location Post-Delivery	
Neonatal Intensive Care Unit	9 (15)
Wellborn Nursery	51 (85)

Table 3

Child Development at 4 months of age. P values by one way ANOVA.

	Gross Motor	Fine Motor	Cognitive	Language	BMI	Observations
Vitamin D	0.0613	0.5330	0.0999	0.5330	0.4483	34
Total T3	0.1516	0.0814	0.3612	0.0814	0.9076	34
Free T3	0.1418	**< 0.01**	0.9148	**< 0.01**	0.2461	34
T3 Uptake	0.6826	0.5368	0.2679	0.5368	0.2566	34
T4	0.8748	0.9294	**< 0.01**	0.9294	0.5927	34
Free T4	0.9499	0.6935	0.2616	0.6935	0.5131	34
TSH	0.5272	0.5973	0.7564	0.5973	0.1669	34
Calcium	0.4497	0.3276	0.9433	0.3276	**< 0.01**	38
Magnesium	0.1601	0.0620	0.8406	0.0620	0.9756	38
Copper	0.8497	0.1146	0.7183	0.1146	0.6083	38
Zinc	0.1305	0.7628	0.1086	0.7628	0.2896	38
Manganese	0.5206	0.2309	0.8007	0.2309	0.4871	38
Lithium	0.5722	0.9362	0.4949	0.9362	0.4135	38
Selenium	0.7396	0.8620	0.7483	0.8620	0.7795	38
Strontium	0.2320	0.2910	0.8227	0.2910	0.6253	38
Molybdenum	0.3986	0.7355	0.7486	0.7355	0.3438	38
Arsenic	0.5429	0.7054	0.8862	0.7054	0.3336	38
Barium	0.3276	0.5572	0.0976	0.5572	0.8471	38
Cadmium	0.2702	0.2909	0.5283	0.2909	0.7939	38
Cobalt	0.0627	0.2451	0.2451	0.2451	0.2898	38
Lead	0.2444	0.6853	**0.0436**	0.6853	0.4628	38
Mercury	**0.0439**	0.7082	0.5797	0.7082	0.5552	38
Nickel	–	–	–	–	1.0000	38
Platinum	0.6294	0.8173	0.8173	0.8173	0.3013	38
Silver	–	–	–	–	1.0000	38
Thalium	–	–	–	–	1.0000	38
Uranium	–	–	–	–	1.0000	38

Table 4

Child Development at 6 months of age. P values by one way ANOVA.

	Gross Motor	Fine Motor	Cognitive	Language	BMI	Observations
Vitamin D	–	0.6687	–	0.6191	0.6276	30
Total T3	–	0.2522	–	0.0914	0.8418	30
Free T3	–	0.0764	–	**< 0.01**	0.5132	29
T3 Uptake	–	0.7887	–	0.5823	0.1159	30
T4	–	0.7168	–	0.8990	0.9018	30
Free T4	–	0.2987	–	0.4546	0.1393	30
TSH	–	0.9028	–	0.6471	0.3210	30
Calcium	–	0.5243	–	0.3469	0.0746	37
Magnesium	–	0.1408	–	**0.0431**	0.7420	37
Copper	–	0.4649	–	0.0717	0.3519	37
Zinc	–	0.5603	–	0.9631	0.4324	37
Manganese	–	0.7371	–	0.3813	0.5603	37
Lithium	–	0.0535	–	0.8982	0.0982	37
Selenium	–	0.8751	–	0.9759	0.3692	37
Strontium	–	0.9021	–	0.2890	0.5100	37
Molybdenum	–	0.2652	–	0.7825	0.3322	37
Arsenic	–	0.5159	–	0.7418	0.3457	37
Barium	–	**0.0120**	–	0.5746	0.9570	37
Cadmium	–	0.8307	–	0.2981	0.7752	37
Cobalt	–	0.4174	–	0.2560	0.5085	37
Lead	–	0.5976	–	0.7131	0.1998	37
Mercury	–	0.5765	–	0.6973	0.1298	37
Nickel	–	–	–	–	1.0000	37
Platinum	–	0.7369	–	0.8149	0.5962	37
Silver	–	–	–	–	1.0000	37
Thalium	–	–	–	–	1.0000	37
Uranium	–	–	–	–	1.0000	37

Table 5

Child Development at 12 months of age. P values by one way ANOVA.

	Gross Motor	Fine Motor	Cognitive	Language	BMI	Observations
Vitamin D	0.7997	0.6212	0.7997	0.2280	0.4107	30
Total T3	0.0856	0.3281	0.0856	0.7370	0.7982	30
Free T3	**< 0.01**	0.4867	**< 0.01**	0.9446	0.1617	29
T3 Uptake	0.5849	0.0701	0.5849	0.8593	0.9843	30
T4	0.7907	0.3435	0.7907	0.3597	0.4704	30
Free T4	0.7980	**0.0108**	0.7980	0.1275	0.7162	30
TSH	0.5193	0.8499	0.5193	0.8022	0.3779	30
Calcium	0.3210	0.2416	0.3210	**0.0391**	**0.0325**	34
Magnesium	0.0818	0.1383	0.0818	0.6007	0.2254	34
Copper	0.2221	**0.0284**	0.2221	0.3080	0.5132	34
Zinc	0.9382	0.8059	0.9382	0.2067	0.8901	34
Manganese	0.3616	0.0565	0.3616	0.6563	0.0514	34
Lithium	0.8581	0.1256	0.8581	0.9903	0.8365	34
Selenium	0.9564	0.1293	0.9564	0.6978	0.9582	34
Strontium	0.3081	0.6654	0.3081	0.2614	0.9546	34
Molybdenum	0.7324	**0.0283**	0.7324	0.9135	0.7175	34
Arsenic	0.7091	0.3523	0.7091	0.3850	0.5064	34
Barium	0.5519	0.1068	0.5519	0.8560	0.1595	34
Cadmium	0.2203	0.2814	0.2203	0.6643	0.7875	34
Cobalt	0.3001	0.9643	0.3001	0.2737	0.0911	34
Lead	0.7625	0.1990	0.7625	0.1335	0.3134	34
Mercury	0.6800	0.6930	0.6800	0.9478	0.2193	34
Nickel	–	–	–	–	1.0000	34
Platinum	0.3321	0.1670	0.3321	**< 0.01**	1.0000	34
Silver	–	–	–	–	1.0000	34
Thalium	–	–	–	–	1.0000	34
Uranium	–	–	–	–	1.0000	34

Table 6

Child Development at 2 years of age. P values by one way ANOVA.

	Gross Motor	Fine Motor	Cognitive	Language	BMI	Observations
Vitamin D	–	**< 0.01**	0.3873	0.9012	0.8877	31
Total T3	–	0.1279	0.4354	0.7872	0.8661	31
Free T3	–	0.1599	0.8661	0.1158	0.5451	30
T3 Uptake	–	0.5042	0.9539	0.9097	0.1721	31
T4	–	0.7789	0.1636	0.8985	0.4188	31
Free T4	–	0.7130	0.4970	0.5824	0.2630	31
TSH	–	0.8077	0.3430	0.6492	0.8290	31
Calcium	–	0.6921	0.5233	0.7971	0.3561	37
Magnesium	–	0.9195	0.8829	0.6559	0.8803	37
Copper	–	0.9383	0.4453	0.7223	0.1834	37
Zinc	–	**< 0.01**	0.8943	**0.0399**	0.5321	37
Manganese	–	0.1705	0.0503	**0.0245**	0.9004	37
Lithium	–	0.3863	0.9118	0.3035	0.9455	37
Selenium	–	0.4328	0.8260	0.3338	0.1891	37
Strontium	–	0.8064	0.9395	0.9395	0.9065	37
Molybdenum	–	0.4810	0.2520	0.1697	0.6069	37
Arsenic	–	0.7704	0.3900	0.3435	0.7576	37
Barium	–	0.5292	0.8676	0.4873	0.9284	37
Cadmium	–	0.4337	0.4499	0.3657	0.1377	37
Cobalt	–	0.1254	0.3317	0.3317	**0.0239**	37
Lead	–	0.3891	**0.0159**	0.8628	0.7448	37
Mercury	–	0.5967	0.6597	**0.0227**	0.0928	37
Nickel	–	–	–	–	1.0000	37
Platinum	–	0.8149	0.7330	0.7330	0.1517	37
Silver	–	–	–	–	1.0000	37
Thalium	–	–	–	–	1.0000	37
Uranium	–	–	–	–	1.0000	37

Table 7

Child Development at 5 years of age. P values by one way ANOVA.

	Gross Motor	Fine Motor	Cognitive	Language	BMI	Observations
Vitamin D	0.8745	0.4009	0.2566	0.5848	0.5052	19
Total T3	0.7038	0.9531	0.2935	0.7199	0.7743	19
Free T3	0.5590	0.1134	0.4715	0.2065	0.8037	18
T3 Uptake	**0.0222**	0.5392	0.7765	0.3549	0.4156	19
T4	0.0691	0.9834	0.4205	0.6047	0.7497	19
Free T4	**0.0172**	0.5264	0.3973	0.5320	0.2995	19
TSH	0.4902	0.5283	0.8179	0.8773	0.0829	19
Calcium	0.0801	0.6623	0.2640	1.0000	0.1370	22
Magnesium	**0.0378**	0.6096	0.2897	0.5616	0.3318	22
Copper	0.1794	0.7898	0.2257	0.8708	0.5126	22
Zinc	0.5745	0.5278	0.2592	0.9695	0.5111	22
Manganese	0.1317	0.6736	0.8656	0.6298	0.8652	22
Lithium	0.5545	0.5705	0.9707	0.1379	0.7115	22
Selenium	**0.0475**	0.6365	0.7094	0.9956	**0.0268**	22
Strontium	0.8600	0.4719	0.4953	0.7474	0.5961	22
Molybdenum	0.1084	0.9748	0.4427	1.0000	0.4952	22
Arsenic	0.1837	0.8548	0.4112	0.9501	0.3858	22
Barium	0.1871	0.8464	0.7074	0.6073	0.8683	22
Cadmium	0.3234	0.2480	0.1065	0.8166	0.4155	22
Cobalt	0.2676	0.8718	0.5148	0.8190	0.1138	22
Lead	0.7651	0.2688	0.2939	0.5681	0.3983	22
Mercury	0.6265	0.7374	0.5353	0.5353	0.9067	22
Nickel	–	–	–	–	1.0000	22
Platinum	**< 0.01**	**0.01**	**< 0.01**	**< 0.01**	1.0000	22
Silver	–	–	–	–	1.0000	22
Thalium	–	–	–	–	1.0000	22
Uranium	–	–	–	–	1.0000	22