

THE IMPACT OF BODY WEIGHT ON THE SECONDARY OSSIFICATION CENTERS DEVELOPMENT AND THE TERM OF CLOSURE OF THE ANTERIOR FONTANELLE IN INFANTS

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ABSTRACT

Introduction: during the infant development, the organ growth is influenced by genetic factors, diet, hormones and many neuropeptides. The secondary ossification center in the hip joint begins to form around the 4th month of life. Primary dentition begins at the age of 5-6 months with the emergence of the central incisor in the maxilla. At birth, 6 fontanelles are present between the plate bones of the cranium. The largest is the anterior or large fontanelle.

Objective of our research is to analyze the development of the secondary ossification center in the femoral head in relation to dentition and closure of the anterior fontanelle closure as well as influence of childrens' birth weight and current weight on these processes.

Methodology: The study included 284 infants, male and female, aged 3 to 8 months. Clinical examination of the musculoskeletal system, anthropometric measurements and ultrasonographic findings of the hip joint were performed at the Pediatric Clinic of the Clinical Hospital Center Pristina in Gracanica.

Results: The development of secondary ossification centre correlated with child's age, dentition, anterior fontanelle closure, birth weight and delivery method, as well as actual body weight. Anterior fontanelle size was inversely related to age, body weight and secondary ossification.

Conclusions: According to regression analysis, body weight is the only factor that has a direct and independent impact on the onset and progression of ossification process. Every additional kilogram of a child's body weight accelerates secondary ossification by 1.3-3.77 times.

Keywords: infant, ossification center, anterior fontanelle, birth weight, body weight

SRPSKI

TUTICAJ TELESNE TEŽINE NA RAZVOJ SEKUNDARNIH CENTARA OSIFIKACIJE I TERMINA ZATVARANJA VELIKE FONTANELE KOD ODOJČADI

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SAŠETAK

Uvod: Na rast i razvoj organa u odojačkom periodu, utiču genetski faktori, ishrana, hormoni i mnogi neuropeptidi. Sekundarni centar okoštavanja u zglobu kuka počinje da se formira oko 4. meseca života. Primarna denticija počinje u dobi od 5-6 meseci pojavom centralnog sekutića u maksili. Prilikom rođenja, između pločastih kostiju lobanje nalazi se 6 fontanela. Najveća je prednja ili velika fontanela.

Cilj našeg istraživanja jeste analiza nastanka sekundarnog centra okoštavanja u glavi femura u odnosu na denticiju i zatvaranje prednje fontanele, kao i uticaj porođajne mase i aktuelne težine deteta na ove procese.

Metodologija: Istraživanjem je obuhvaćeno 284 odojčeta, muškog i ženskog pola, uzrasta od 3 do 8 meseci. Klinički pregled mišićno-skeletnog sistema, antropometrijska merenja i ultrazvučni nalaz zgloba kuka obavljen je na Pedijatrijskoj klinici Kliničko-bolničkog centra Priština u Gračanici.

Rezultati: Razvoj sekundarnog centra okoštavanja u korelaciji je sa uzrastom deteta, denticijom, veličinom prednje fontanele, porođajnom težinom i načinom porođaja, kao i aktuelnom telesnom masom. Veličina prednje fontanele bila je negativnoj korelaciji sa uzrastom, telesnom težinom i sekundarnom osifikacijom

Zaključci: Prema regresionoj analizi, telesna težina je jedini faktor koji ima direktan i nezavisan uticaj na početak i progresiju procesa okoštavanja. Svaki dodatni kilogram telesne težine deteta ubrzava sekundarnu osifikaciju za 1,3-3,77 puta.

INTRODUCTION

Growth is a dynamic and complex process. One of the parameters used to monitor the development and maturity of the skeletal system is the ossification of bones and the creation of ossification centers [1].

The bones are built of a dense bone matrix created by active osteoblasts. After being surrounded by the matrix osteoblasts enter the rest state and are called osteocytes; due to formation numerous cytoplasmatic protractions, osteocytes gradually gain stellate [2]. Osteoblasts secrete extracellular matrix, osteocytes control bone maintenance and repair, and osteoclasts break down bone tissue [3].

The formation of endochondral bone takes place primarily in areas exposed to stress. Therefore, this endochondral bone can primarily be found in the bones of the joints and the base of the skull. The matrix then undergoes calcification and the cells consequently degenerate. Region known as primary ossification center is created during the second and third months of fetal development. Primary ossification center is the first area of bone where ossification begins. It usually occurs in the central part of each developing bone. In long bones, the primary centers occur in the diaphysis.

Meanwhile, as bone tissue progressively replaces cartilage in the diaphysis, chondrocytes and cartilage continue to grow at the ends of the bone creating future epiphyses. After birth [4], the same series of events (matrix mineralization, chondrocyte degeneration, capillary proliferation, and osteoblast activation) occur in the epiphyseal regions, creating secondary ossification centers.

All ossification centers merge between the ages of 14 and 18 [5]. The proximal femoral ossification center and its cartilaginous anlage continue to enlarge until adult life, at which time only a thin layer of articular cartilage remains.

In the oral cavity, deciduous incisors erupt first, followed by the mandibular and maxillary molars (after 3-4 months), and canines (after another 3-4 months). Once the second molars in both jaws emerge at 24-30 months, the deciduous dentition is completed [6].

At birth, an infant has six fontanels. The anterior fontanel or big fontanel is the largest and most important for clinical evaluation. It is located at the junction of the frontal and parietal cranial bones and closes at 8-24 months, usually around 18 months of age.

STUDY OBJECTIVE

The aim of this study was to determine the correlation between the formation of the secondary ossification center in the hip joint with the beginning of primary dentition, e.g.,

the emergence of the first central incisor in the mandible and the development of the anterior fontanelle. Also, with this study, we wanted to determine the connection between the formation of the secondary ossification center and the current children's body weight, as well as the birth weight.

METHODOLOGY

The study included 284 infants, male and female, aged 3 to 8 months. Clinical examination of the musculoskeletal system and ultrasonographic finding of the hip joint were performed at the Pediatric Clinic of the Clinical Hospital Center Pristina / Gračanica, in the clinical outpatient clinic and the cabinet for ultrasonography.

The relevant anamnestic data included birth weight and length, the mode of delivery (natural or operative) as well as the Apgar score in the first and fifth minute after birth.

Anthropometric measurements included body weight and height measured with the use of digital scales and meters. The size of the fontanelles was measured and recorded as mean length (front and back dimension) and width (transverse dimension). This assessment is used together with the head circumference measurement as an index of cranial development from birth and to the second year of life.

To assess the occurrence of a secondary ossification center in the femoral head we applied hip joint ultrasonography. We used Logiq C5 ultrasound with the 5 MHz linear probe. This assessment is part of the preventive examination of the child and is performed at the age of 6 weeks - 5 months. Ultrasonographic examination provides insight into the soft tissue structures of the muscles, tendons and joint capsule, cartilage, as well as the bone elements - acetabulum and the femoral head.

Dental age may be determined both radiographically and clinically by observing tooth emergence. We used visual method for the assessment of primary dentition stage.

Based on anamnestic data as well as clinical and psychomotor development assessment, we excluded infants with genetic, metabolic, or acquired disorders that might influence the normal development of calvary bone development and cranial fontanelle closure.

Statistical processing included Student's T- test for small independent samples, x2 test, univariate linear regression, and multivariate ordinal logistic regression. To avoid redundancy and/or singularity of data within multivariate model, only the variables with regression coefficient >0.2 on univariate regression might enter the multiple ordinal logistic regression.

RESULTS

This research included 284 children, male and female, aged 3-8 months, who were examined in the Pediatric Clinic of KBC Pristina in Gracanica.

The average age was 4.49 ± 1.7 months, and girls were more prevalent (164 female vs. 120 male children); the average anterior fontanel size was 4.36 ± 4.14 cm². Initial primary dentition was determined in 77 children, while 207 children had no signs of tooth eruption. The largest number of children were born naturally (180), and 104 births were completed by surgical procedure. The largest number of examined infants were born after a full 37 gestational weeks, while 7.14% of them had pre- or post-term birth.

Table 1: General characteristics of the patients

PARAMETER	UNIT	VALUE
Age	months	4.49 ± 1.7
Gender	male female	120 164
Anterior fontanelle (AF)	(cm ²)	4.36 ± 4.14
Dental eruption	absent present	228 56
Secondary center of ossification	absent present	114 170
Childbirth delivery	Caesarean section Natural childbirth	104 180
Gestation age	Term newborn Premature newborn Post term newborn	264 16 4
Apgar I	Apgar: 8,9,10 Apgar: 5,6,7 Apgar: 1,2,3,4	268 10 6
Apgar II	Apgar: 8,9,10 Apgar: 5,6,7 Apgar: 1,2,3,4	262 18 4
Body weight	(kg)	6.3 ± 1.39
Birth weight	(kg)	3.3 ± 0.55

The relevant characteristics of patients are displayed at the table 1. Two hundred and sixty-eight children in our study had excellent Apgar score in the first minute (8.9 to 10) in 268 children within our study. An unfavorable Apgar grade (5.6 - 7) at birth was registered in 10 (0.36%) children while Apgar values of 1,2,3 or 4 in the first minute after birth had 6 children (0.14%). In the 5th minute after delivery, our participants' Apgar scores were similar.

Based on the presence of ossification center in the femoral head, the examined children were divided into two research groups (Table 2). The first group consisted of 170 children in whom the formation of secondary ossification center was diagnosed by ultrasonography. The second research group consisted of 114 infants, in whom the ossification grain was not visualized.

Table 2: Results of the T- and Chi-square tests of the difference in potential factors that may influence ossification between the two groups

	SECONDARY OSSIFICATION CENTER (SOC)		UNFORMED OSSIFICATION CENTER		
Age (months)	3.96 ± 1.68 mes.		4.07 ± 1.34		p > 0.05
Gender	Male	67 (39.11%)	Male	46 (40.35%)	
	Female	103 (60.89%)	Female	68 (59.65%)	
Total	170 (99.99%)		114 (100%)		p > 0.05
Anterior Fontanelle (cm ²)	2.49 ± 1.86		2.00 ± 2.12		p > 0.05
Dental eruption	57 (33.53%)		22 (19.29%)		p < 0.05
Childbirth delivery	Cesarean surgery	48	Cesarean surgery	56	p > 0.05
	Natural unassisted childbirth	64	Natural unassisted childbirth	116	
Gestation age	Term newborns	110 (64.71%)	Term newborns	154 (74.03%)	p > 0.05
	Premature newborns	8 (4.71%)	Premature newborns	8 (7.02%)	
	Post term newborn	2 (1.18%)	Post term newborn	2 (1.75%)	
APGAR I (Mean value)	8.94 ± 0.87		8.84 ± 1.32		p > 0.05
APGAR II (Mean value)	8.21 ± 0.8		8.27 ± 1.33		p > 0.05
Weight (kg)	6.79 ± 1.14		5.54 ± 1.43		p < 0.001
Birth weight (kg)	3.28 ± 0.631		3.31 ± 0.508		p > 0.05

The infants who entered our study were 3 to 8 months old, (which is the time for the first or second regular hip ultrasonographic examination) and there was no significant difference in age between the two research groups. There was no significant difference by gender either. In the group of children without the ossification center 40.35% of children were male and 59.65% female; in the group in which the ossification centers the gender distribution was 39.11% and 60.89%, respectively.

Tooth eruption was visualized in 22 (19.29%) infants without and 57 (33.53%) of those with formed secondary ossification center (p < 0.05).

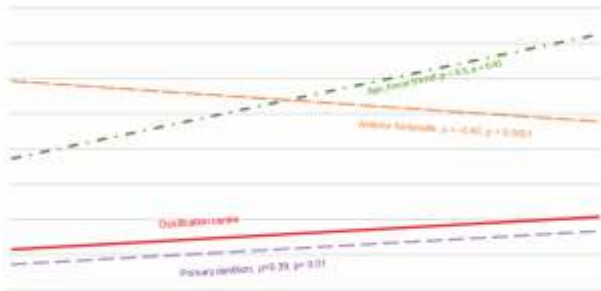
The largest number of children within both examined groups were born as term infants (90% of children without ossification center, and 92.77% in the other group). The Apgar score in the first and fifth minute after the birth also had an even distribution, and there was no significant difference between the groups (8.94 ± 0.87 , 8.84 ± 1.32 , p > 0.05).

The current body mass of the child was directly related to the formation of the ossification center. The average weight of the child in the group without ossification center was 5.54 ± 1.43 kg, and in another group 6.79 ± 1.14 kg (p < 0.001). On the other hand, statistical analysis showed that the birth weight of newborns with and without ossification centers was not substantially different. (3.31 ± 0.508 and 3.28 ± 0.631 kg, respectively, p > 0.05).

The average size of the large fontanelle was similar in both groups (2.49 ± 1.86 cm² and 2.003 ± 2.12 cm², p > 0.05). Also, the difference in distribution of the patients according to the size of anterior fontanel in two groups was non-significant (Wilcoxon rank test).

The difference related to the mode of the delivery was non-significant. The largest number of children were born naturally (57.14% in the first examined group and 67.05% in the second, p > 0.05).

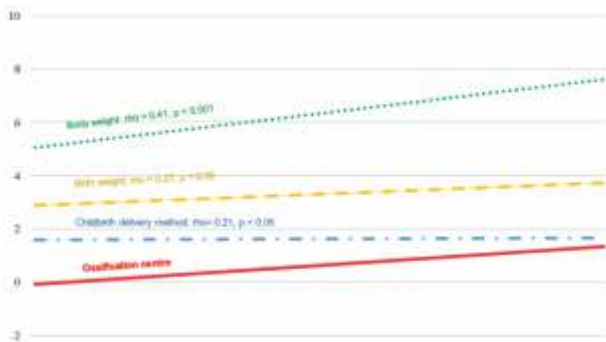
Figure 1: Correlation of the development of the femoral secondary ossification center with age, primary dentition, and the size of the anterior fontanelle



* ρ - Spearman's correlation coefficient
* p - probability, indicating statistical significance of the correlation

There is a significant relationship (Figure 1) between the presence of the ossification center and age ($\rho=0.5$, $p<0.01$), as well as secondary ossification and primary dentition ($\rho=0.39$, $p<0.01$) in our study. The creation of the ossification center was inversely related to the size of the anterior fontanelle ($\rho=0.4$, $p<0.0001$).

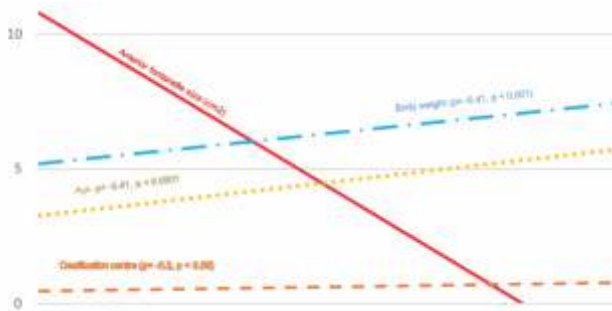
Figure 2: Correlation of the development of the femoral secondary ossification center with body weight, birth weight and childbirth delivery mode



* ρ - Spearman's correlation coefficient
* p - probability, indicating statistical significance of the correlation

The existence of an ossification center in the femoral head was directly related (Figure 2) to the child's actual body weight ($\rho=0.41$, $p<0.001$). The correlation with the birth weight and childbirth delivery mode was weak, although significant. It is an interesting fact that the early existence of the center of ossification is related with the type of the delivery - natural or operative.

Figure 3: Correlation of the anterior fontanelle size with body weight, age and formation of the secondary ossification center



* ρ - Spearman's correlation coefficient
* p - probability, indicating statistical significance of the correlation

As presented at figure 3, the size of anterior fontanelle was significantly inversely related with body weight ($\rho=-0.41$ and the development of the secondary ossification center ($\rho=-0.2$, $p<0.05$). The correlation with body weight was highly significant ($p<0.001$).

Table 3: Results of the ordinal regression analysis of the relation between the formation of the ossification center formation and the relevant* variables

Parameter	Estimate	Standard error	Wald	P	O.R.	CI lower	CI upper
Dentition	0.001	0.82	0.792	$p > 0.05$	0.48	0.09	2.52
Anterior fontanel	0.085	0.09	-0.089	$p > 0.05$	1.09	0.91	1.30
Delivery mode	-0.88	0.65	1.874	$p > 0.05$	2.43	0.68	8.74
Body weight	1.02	0.3	0.1	$p < 0.01$	2.4	1.03	3.77

*variables with univariate regression coefficient > 0.2 entered the multivariate ordinal regression procedure

*Wald - the result of Wald's chi-square test of the regression coefficients within ordinal logistic regression

*O.R. - odds ratio

*CI - confidence interval

* p -probability indicating statistical significance of the regression

Ordinal logistic regression analysis at table 3, shows that among the factors examined in the study, only body weight has a direct and independent influence on the formation and progression of ossification center: its influence is statistically measurable even when all other factors are constant ($p < 0.01$). From the analysis, it is also noticeable that each kilogram added to the child's body weight accelerates the development of secondary ossification between 1.3-3.77 times.

DISCUSSION

During growth, various systems in the body undergo changes and gradually mature. The development and maturation of organs and organ systems in the child's body occur at a certain dynamic. The epiphysis surrounds the physis at both ends of the long bone. When one epiphysis of the bone articulates with another, a joint is formed. The epiphyseal physis is responsible for longitudinal growth. Almost all epiphyses in newborns are cartilaginous and thus not visible by standard radiography. Secondary ossification centers frequently form within the cartilaginous epiphysis, allowing the epiphysis to grow in all directions through endochondral ossification. The number and location of the ossification centers, on the other hand, differ from one another [7]. The epiphysis at each end of most long bones contains a secondary ossification center, but some have them on the one side only.

The predictable ossification centers progressions may serve as the reference for skeletal maturation assessment. Long bones develop until the epiphyses fuse with the metaphysis at the growth plates. This growth plate fusion occurs at the different times in each bone [8]. Delayed pelvic ossification may be generalized or focal. Generalized is mainly caused by endocrine disorders, malnutrition, chronic diseases or chromosomal abnormalities; the focal delay may occur as the result of many bones developmental disorders. It occurs primarily in the epiphyses [9].

The ossified nucleus in the epiphysis of the femoral head may exist at birth, but most often it occurs subsequently, in the infantile period (5-8th month). Its

absence up to 10 months of the child's life indicates hip dysplasia [10].

The center of ossification in the femoral head develops between 20-28 weeks of life. It was discovered that, among other things, ethnical association influences its genesis. According to study of A. Cziger et al, performed in a large group of children of various nationalities, 81 percent of the tested Indian newborns had a formed ossification center at the age of 20 weeks, whereas only 22.74 percent of the Israeli infants had established ossification grains at that age. Also, 90 percent of the infants in both groups [11] developed ossification centers in the femoral head in the period 20-24 weeks.

Analysis of bone development and the appearance of ossification centers [12] may provide useful information in a variety of clinical settings. The ossification center of the epiphysis in the femoral head is an essential radiographic feature in the newborn hip. Between the sixth and eighth months of life, this developmental milestone becomes evident radiographically. Diet, genetics, hormones, and chronic illness all may have an impact on the course of skeletal and bone maturation. Factors that accelerate the ossification process are increased secretion of growth hormone, thyroxine, and higher serum calcitonin concentrations, while parathyroid hormones, sex hormones, ACTH and hypercortisolemia have an inhibitory effect on the ossification process.

The bone age of a child reflects the level of biological and structural maturity better than the chronological age determined from the day of birth [13].

Dental maturity has been widely used for forensic purposes, but data on its application in the diagnosis and follow-up of endocrine disorders is limited. This is most likely due to the fact that the rate of teeth calcification is far less impacted by diet and hormonal activity than mineralization in extremity bones [14]. Two techniques similar to those used for hand bones are employed to estimate dental age.

The term "eruption" refers to the permanent ascent of the tooth from the maxillary bones to the alveolar ridge and up to the occlusal surface, whereas the term "emergence" refers to the piercing of the gum and the first appearance of the tooth in the oral cavity, which is a transient event of very short duration. Only radiography can evaluate the ongoing dental maturation process. Increased BMI levels at early life indicate accelerated dental growth at later age, demonstrating that BMI has a long-term influence on dental development. Obese children often require early orthodontic treatment. These findings support earlier research, adding to the reports that very early teeth eruption is a common effect of childhood obesity [15].

The anterior fontanel is 2.1 cm in size on average. The median age [16] of anterior fontanelle closure is 14 to 16 months, with 90% to 96% closing by 24 months of life.

An undersized fontanel could be caused by brain development retardation, craniosynostosis, or

hyperthyroidism. An enlarged fontanel without increased cranial pressure may be a hallmark of a number of medical conditions, including skeletal anomalies (e.g., achondroplasia, cleidocranial dysostosis, osteogenesis imperfecta, chromosomal anomalies (e.g., trisomy 9p, 13, 18, 21), hypothyroidism, or intrauterine malnourishment; [17] in the latter condition, anterior fontanel size was related to reduced epiphyseal ossification.

At term, male newborns had significantly larger anterior fontanelles than female neonates [18], and anterior fontanelle size is strongly connected to birth weight and head circumference.

Other studies [19] like ours, have found no gender differences in the age of ossification center development.

Duc et al [20] found no considerable differences in size or age at anterior fontanel closure between term and preterm newborns, or between genders. Fontanel size was adversely related to weight and length in post-term infants, although only a few of these relationships were statistically significant. There were no significant associations between anterior fontanel size and head circumference measurements or bone maturity. The age of the anterior fontanel closure was also unrelated to either the growth characteristics or bone age.

Newborns are 74.4% less likely to deviate from normal fontanelle dimensions than premature babies. The way a child is born determines the dimensions of the fontanelle. The explanation lies in the passage of the newborn through the birth canal, and therefore, vaginally born newborns have a 64.2% lower probability of having an enlarged anterior fontanelle than newborns born by caesarean section [21,22].

According to previous studies [21,22] the diameter of the anterior fontanelle is predominantly influenced by the birth weight; in addition, it is also affected by gestational age, method of delivery, and head circumference.

Total body length and the rate of ossification of the various centers have a strong relationship. Identical, although less direct relationship was found between the rate of bone formation and body mass [23].

CONCLUSION

The creation and development of secondary ossification center in the femoral head correlates with dental development, the age of the child, primary dentition, closure of the anterior fontanelle, and mode of delivery. Birth weight may also influence the onset of ossification and bone maturation. According to regression analysis, body weight is the only factor that has a direct and independent impact on the onset and progression of ossification process. Every additional kilogram of a child's body weight accelerates secondary ossification by 1.3-3.77 times.

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IZJAVA O AUTORSTVU

Svi autori ovog rada izjavljuju da nemaju finansijsku niti bilo kakvu materijalnu dobit od objavljivanja rezultata ovog istraživanja

DOPRINOSI AUTORA:

Snežana Marković Jovanović- Koncept, dizajn studije, klinički odabir ispitanika i ehosonogafski pregled
 Aleksandar Jovanović - statistička obrada podataka, prevod rukopisa na engleski jezik
 Stolić Radojica- pretraživanje literature, izrada teksta
 Popović Milica- priprema podataka za statističku obradu, uređjivanje teksta
 Danijela Ivanović- izrada tabela, grafikona, finalna obrada rada