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The relationship between maternal serum apelin-36 level and anthropometric indices up to 18 months after birth; A Cohort Study

Relación del nivel de apelina-36 en suero materno con índices antropométricos del lactante hasta los 18 meses de edad; Estudio de cohorte

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Abstract

BACKGROUND & OBJECTIVE: Apelin plays an important role in regulating energy intake and homeostasis. This study aims to investigate the relationship between maternal serum apelin-36 and infants' anthropometric markers up to 18 months after birth.

MATERIAL & METHODS: In this cohort study, 166 pregnant women aged 18-40 years old third trimester period referred to the Prenatal Clinic, participated in this study. The women were divided into two groups: an elective cesarean section group (as an exposure; n = 23), and a vaginal delivery group (as a non-exposure; n = 22). Maternal serum Apelin-36 levels were measured during the third trimester period and after delivery using ELISA. Infants were followed for up to 18 months during the postpartum period.

RESULTS: The serum level of Apelin-36 after delivery was significantly and positively correlated with the weight of infants at 12 months, and 18 months $P<0.05$. It was also correlated with the height of infants at 6 months $P<0.05$ and 18 months $P<0.05$. Additionally, Apelin-36 was significantly correlated with the head circumference at 12 months $P < 0.05$.

CONCLUSIONS: The maternal serum Apelin-36 level showed a relationship with the infant's anthropometric indicators and gender.

KEYWORDS: Apelin-36, pregnant women, Obstetric delivery, caesarean section, Newborn infant

Resumen

ANTECEDENTES Y OBJETIVO: La Apelina juega un papel importante en la regulación de la ingesta energética y la homeostasis. El objetivo de este estudio fue investigar la relación entre la apelina-36 en suero materno y los marcadores antropométricos de sus bebés hasta 18 meses después del nacimiento.

MATERIAL Y MÉTODOS: En este estudio de cohorte participaron 166 gestantes del tercer trimestre de 18 a 40 años remitidas a la Clínica Prenatal. Las mujeres se dividieron en dos grupos: un grupo de parto vaginal (n = 22) y un grupo de cesárea electiva (n = 23). Los niveles de apelina-36 en suero materno se midieron durante el período del tercer trimestre y después del parto mediante ELISA. Los bebés fueron seguidos hasta por 18 meses durante el período posparto.

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RESULTADOS: El nivel sérico de apelina-36 después del parto se correlacionó de manera significativa y positiva con el peso de los lactantes a los 12 meses y a los 18 meses P < 0,05. También se correlacionó con la altura de los bebés a los 6 meses P < 0,05 y a los 18 meses P < 0,05. Además, la apelina-36 se correlacionó significativamente con el perímetro cefálico a los 12 meses P < 0,05. El análisis mostró que la apelina-36 sérica tiene relación con el peso del lactante a los 12 y 18 meses, y la altura a los 6 y 18 meses en el grupo de parto natural.

CONCLUSIONES: El nivel sérico materno de apelina-36 mostró una relación con los indicadores antropométricos y el género del lactante

PALABRA CLAVE: Apelina, Mujeres Embarazadas, Cesárea, Parto Obstétrico, Recién Nacido.

BACKGROUND

Apelin is a regulatory peptide, identified in 1998 by Professor M. Fujino's team and is encoded by the *APLN* gene in humans which is located on chromosome Xq 25-26.[1]

Apelin has been described as an endogenous ligand for the APJ receptor, And Apelin-36 and Apelin-13 are two active molecular forms of Apelin that have the highest biological activity. Moreover, the extensive-expression of apelin and its receptors in various tissues indicate a very extensive role of this hormone in the body.[2-5] Apelin is an endocrine, paracrine, and autocrine agent. Sex-steroids, insulin, TNF-α (Tumor Necrosis-Factor Alpha), and growth hormone up-regulate apelin expression in the adipose tissues of humans and mice.[6-15] Furthermore, it is responsible for the regulation of food intake, as well as fluid balance in the hypothalamus.[16]

Pregnancy is a dynamic process during which one or more fetuses grow. The development and growth of the embryo depend on the correct formation of the placenta, which allows the transfer of nutrients and oxygen from the mother to the fetus.[17] Disrupting the formation of the placenta leads to pregnancy-related disorders such as IUGR.[18] Apelin is essential for the formation of the embryo's cardiovascular system and early placental development.[17] Given the role of apelin in the regulation of cardiovascular function, it seems to have a potential role in modulating normal blood vessel growth in the organs, especially in sexual organs,[19] that play a role in the development of the fetus and child.[20]

As mentioned above, the expression of Apelin in many organs has pleiotropic effects like the regulation of food intake, body weight, or cardiovascular and immune function.[21] Studies suggest that the presence of compounds like Apelin in human breast milk can influence food intake and energy balance.[20] Apelin is also involved in the regulation of infant growth and related to the development of metabolic disorders in the future.[20]

To gain further insight into the role of apelin-36 in the growth of the infant up to 18 months after birth, we investigated the relationship between the maternal level of apelin-36 and the infant's gender and anthropometric indices of the newborn until 18 months after birth. We were particularly interested in the mode of delivery – i.e., vaginal delivery vs. cesarean section – as no study to date has investigated this area.

MATERIALS AND METHODS

The participants of this study were 166 pregnant women aged 18-40 years old referred to a prenatal clinic of Mahdieh Hospital in Tehran which was selected by a convenience sampling method during their third trimester of the period.[22] Informed consent was obtained before they were enrolled in the study. As mentioned in our previous article,[22] after delivery, participants were divided into two subgroups according to delivery mode (**caesarean** (CS) group [As an exposure; n = 23) and vaginal

delivery (VD) group (as a non-exposure; n = 2]). Non-fasting venous blood was collected from participants during the 28th-32nd gestational weeks and in the first 24 hours after delivery. Then, they all followed up as a cohort study until 18 months after birth. We measured the anthropometric indices of the children (height, weight, and head circumference) at birth and at 2, 4, 6, 12, and 18 months to recognize whether height, weight and head circumference were affected by maternal serum apelin or not.

In the terms of follow-up, we lost 3 participants because of non-respond, being out of reach due to changing their location. So, 21 participants remain in each group.

Instruments and Analysis

The head circumference of the child (the circumference of the most prominent point of the occiput to the broadest part of the forehead above the eyebrow, so that the meter is placed above the ears) was measured by using a non-stretchable tape meter with a precision of 0.1 cm. Measurements of height and weight were performed using a Baby Length Height Measuring Mat in a lying position (with a precision of 0.1 cm) and a digital scale (accurate to 0.1 kg), respectively.

As verified by statistical tests, the two groups were homogeneous in terms of underlying and demographic variables including age, job, education of pregnant mothers and their spouses, fertility status (number of pregnancies, abortions, live and dead deliveries), income, gestational age (in weeks) at the time of the first sample, gestational age at the time of delivery (in weeks), feeding method of infants (formula, breast milk, or both) and neonatal gender status **(Table 1- 3)**.

Kolmogorov-Smirnov test was used to assess the normal distribution of variables in each group. A chi-squared test was used to examine

Table 1. Demographic details of mothers (n=42)

Variable		Type of Delivery		Type of Statistical	P-value
	Category	CS n (%)	VD n (%)		
Maternal education	Undergraduate education	10(47.6)	8(38.1)	Chi-square	0.533
	Tertiary education	11(52.7)	13(61.9)		
Spouses' education	Undergraduate education	14 (66.7)	8 (38.1)		0.064
	Tertiary education	7 (33.3)	13(61.9)		
Maternal Job	Employment	20 (95.2)	17 (81)	Fisher Exact Test	0.343
	Housewife	1 (4.8)	4 (19)		
Spouses' Job	Employment	16 (776.2)	16 (76.2)	Fisher Exact Test	1.000
	Unemployment	5 (23.8)	5 (23.8)		
Family income	> 10 milion RIs	21 (100)	17 (81)	Fisher Exact Test	0.107
	< 10 milion RIs	ho	4 (19)		
Number of delivery	***0***	1 (4.8)	12(57.1)	Chi-square	0.001
	1	17(81)	7 (33.3)		
	2	3 (14.3)	1 (4.8)		
	> 3	0	1 (4.8)		

Number of pregnancy	***1***	1 (4.8)	10 (47.6)	Chi-square	0.019
	2	15 (71.4)	8 (38.1)		
	3	3 (14.3)	1 (4.8)		
	4	2 (9.5)	1 (4.8)		
	5	0	1 (4.8)		
Number of abortions (both spontaneous and induced)	***0***	17 (81)	17 (81)	Chi-square	1.000
	1	3 (14.3)	3 (14.3)		
	> 2	1 (4.8)	1 (4.8)		
Breastfeeding status(the first 6 months)	***Breastfeeding***	19 (90.5)	19 (90.5)	Fisher Exact test	1.000
	breast-milk substitutes	2 (9.5)	2 (9.5)		
Breastfeeding (after 6 month)	***Breastfeeding and complementary food***	20 (95.2)	19 (90.5)	Fisher Exact Test	0.237
	breast-milk substitute and complementary food	1 (4.8)	2 (9.5)		
Fetus gender	***Female***	10 (47.6)	11(52.4)	Chi-square	0.758
	male	11 (52.4)	10(47.6)		

Table 2. Demographic details of mothers (n=42)

Variable	Type of Delivery		Statistical Test
	VD (Mean ± SD)	CS (Mean ± SD)	Independent T test
Maternal Age (year)	28.5 ± 19.21	28.67 ± 4.35	p= 0.750
Gestational age (year)	30.67 ± 2.44	30.1 ± 7.9 y	p= 0.720
Maternal BMI before pregnancy	23.53 ± 2.9	24.74 ± 3.7	p= 0.248
Maternal BMI Delivery time	28.02 ± 2.69	29.60 ± 4.09	p=0.145
Maternal BMI follow up	23.266 ± 3.75	24.83 ±4.35	p= 0.219

Table 3. Determination of the relationship between serum level of maternal Apelin-36 (nmol/L) in the third trimester of pregnancy and the first 24 hours after delivery with a number of pregnancies and number of delivery by type of delivery (N = 42)

Type of delivery	Variables	Number of pregnancy	Number of delivery
VD	***Apelin in the third trimester of pregnancy***	r = 0.135 (P = 0.558)	r = -0.262 (P = 0.251)
	Apelin in the first 24 hours after delivery	r = 0.208 (=0.365)	r = -0.144 (P = 0.532)
CS	***Apelin in the third trimester of pregnancy***	r = 0.135 (P = 0.558)	r = -0.262 (P = 0.251)
	Apelin in the first 24 hours after delivery	r = 0.208 (P = 0.365)	r = -0.252 (P = 0.271)

the association between qualitative variables. Paired-sample t-tests and independent-sample t-tests were used to examine intra-group variations and the difference between groups, respectively. For all statistical tests, the level of significance was considered as $p < 0.05$. Data analysis was done using SPSS software.

Findings

Relation of apelin-36 to fetus/child anthropometric indices

The mean value of maternal serum Apelin-36 level (nmol/L) during the third trimester period and the first 24 hours after delivery in VD were 101.5 ± 105.65 and 84.86 ± 93.64 ($p = 0.029$) respectively. Besides, the mean value of this hormone in CS was consecutively 70.86 ± 86.05and 72.39 ± 97.90 ($p = 0.751$). The physical characteristics of newborns till 18 months for the two groups are summarized in **table 4**. The means of children's anthropometric indices were not significantly different between the two groups ($p > 0.05$), **(table 4)**.

Regarding maternal apelin-36 serum level, there was no significant relationship between birth weight, birth head circumference, birth height, and apelin level in the VD group ($p > 0.05$), **(table 5)**. There was also no significant relationship between weight, head circumference of 2, 4, 6 months, and apelin in the VD group ($p > 0.05$), **(table 5)**. However, results revealed that the maternal serum level of apelin-36 had significant positive correlations with the height

Table 4. The difference in birth weight (g), birth height (cm) and birth head circumference (cm) up to 18 months in the CS group compare with VD

Variables	VD group (n=21) Mean ± SD	CS group (n=21) Mean ± SD	Independent Samples Test
Birth weight (g)	3320.95 ± 320.295	3234.29 ± 461.309	p = 0.484
Weight at 2 months (g)	5309.52 ± 499.91	5423 ± 725.88	p = 0.553
Weight at 4 months (g)	6890.48 ± 919.19	6909.52± 693.473	p = 0.556
Weight at 6 months (g)	7866.67 ± 786. 98	7961.90 ± 786.977	p = 0.940
Weight at 12 months (g)	9295.24 ± 761.89	9542.86 ± 1040.467	p = 0.705
Weight at 18 months (g)	10909.00 ± 638.67	10797.62 ± 1077.552	p = 0.384
Birth height (cm)	50.14 ± 1.49	50.667 ± 2.48	p = 0.411
Height at 2 months (cm)	56.57 ± 1.96	57.286 ± 3.00	p = 0.367
Height at 4 months (cm)	62.09 ± 2.64	62.667 ± 2.90	p = 0.509
Height at 6 months (cm)	67.38 ± 2.44	67.381 ± 3.40	p = 0.717
Height at 12 months (cm)	74.45 ± 3.04	74.381± 4.080	p = 0.949
Height at 18 months (cm)	80.31 ± 3.25	81.143 ± 4.35	p = 0.486
Birth head circumference (cm)	35.12 ± 1.34	34.76 ± 1.77	p = 0.467
Head circumference at 2 months (cm)	38.25 ± 177	38.24 ± 1.37	p = 0.699
Head circumference at 4 months (cm)	40.52 ± 1.55	41.048 ± 1.71	p = 0.306
Head circumference at 6 months (cm)	42.52 ± 1.45	42.60 ± 1.83	p = 0.549
Head circumference at 12 months (cm)	44.93 ± 1.73	45.05 ± 2.11	p = 0.527

at 6 and 18 months ($p < 0.05$). there was no significant relationship between the maternal serum level of apelin-36 and height at 2 and 4 months of age ($p > 0.05$), **(table 5)**.

On the other hand, maternal apelin-36 level showed a positive relationship with the weight at 12 ($p < 0.05$) and 18 ($p < 0.05$) months of age in the VD group, **(table 5)**. There was also a positive correlation between the maternal serum level of apelin-36 and Head circumference at 12 months ($p < 0.05$). The correlation analysis showed that maternal serum apelin-36 level has no relation to children's anthropometric parameters in the CS group ($p > 0.05$), **(table 5)**.

DISCUSSION

Based on the previous study[22], the participant divided into two groups after delivery (VD Group

Table 5. The relationship between maternal serum apelin-36 levels(nmol/L) and anthropometric indices

Anthropometric indices	VD group (n=21)				CS group (n=21)			
	Apelin in the third trimester of pregnancy		Apelin in the first 24 hours after delivery		Apelin in the third trimester of pregnancy		Apelin in the first 24 hours after delivery	
	r	p	r	p	r	p	r	p
Birth weight	0.13	0.57	0.19	0.46	-0.13	0.56	-0.18	0.41
Weight at 2 months	0.32	0.15	0.33	0.13	0.22	0.32	0.18	0.43
Weight at 4 months	0.25	0.27	0.23	0.31	0.29	0.19	0.23	0.29
Weight at 6 months	0.25	0.28	0.22	0.34	0.02	0.90	-0.05	0.83
Weight at 12 months	0.59	0.005*	0.50	0.01*	0.02	0.93	-0.04	0.85
Weight at 18 months	0.66	0.001*	0.61	0.004*	-0.05	0.81	-0.10	0.66
Birth head circumference	-0.24	0.28	-0.23	0.29	0.17	0.44	0.14	0.53
Head circumference at 2 months	-0.02	0.92	-0.04	0.84	0.19	0.39	0.20	0.37
Head circumference at 4 months	0.18	0.41	0.14	0.54	0.10	0.65	0.11	0.61
Head circumference at 6 months	0.35	0.11	0.29	0.19	0.10	0.68	0.09	0.66
Head circumference at 12 months	0.49	0.02*	0.42	0.05	0.18	0.42	0.20	0.37
Birth height	0.34	0.12	0.39	0.07	0.05	0.81	-0.01	0.94
Height at 2 months	0.36	0.10	0.34	0.12	0.40	0.06	0.37	0.09
Height at 4 months	0.42	0.056	0.32	0.14	0.34	0.12	0.32	0.14
Height at 6 months	0.61	0.003*	0.50	0.02*	0.25	0.25	0.23	0.29
Height at 12 months	0.55	0.009*	0.48	0.02*	0.19	0.39	0.19	0.39
Height at 18 months	0.56	0.008*	0.54	0.01*	0.80	0.66	0.11	0.62

and CS group). Regarding this cohort study, we followed up the babies born up to 18 months after birth and measured infants' anthropometric indices in the mentioned groups.

Relation of Apelin-36 to fetus-child anthropometric indices

No study has yet been done to investigate the relationship between maternal serum apelin-36 level and the child's anthropometric markers up to 18 months after birth by categorizing mothers based on the mode of delivery. As I mentioned above, statistical analysis surrounding apelin relation with anthropometric indices of newborns is limited. Nevertheless, three published data are as follows, Cekmez et al. research showed apelin levels significantly elevated in the LGA (Large for Gestational Age) group. As well, apelin was correlated positively with birth weight.[23] And also According to Aslan's investigation that measured maternal serum and cord blood apelin-36 levels at the time of birth, levels of maternal serum apelin-36 positively correlated with cord blood levels. However, Levels of maternal serum and cord blood apelin-36 negatively correlated with birth weight.[24] The findings of mentioned above studies are not in line with each other and also with our research. According to the analysis, no relationship was observed between maternal apelin-36 level and birth weight. This is also consistent with a study by Malamitsi-Puchner et al.,[25] which measured concentrations of plasma apelin in 40 mothers and their singleton full-term babies and neonates on days 1 and 4 of life. Not only this research reveals that there is no relation between birth weight and apelin concentration but the relationship with gender, parity, or mode of delivery has been refused. They also concluded that the postnatal increase of apelin concentrations could be a sign of a gradual initiation of ex utero angiogenesis.[25]

However, according to analysis, this hormone did not correlate with anthropometric indices of the infant in the cesarean delivery group, the positive linear relationship has been indicated between apelin and the weight, height and head circumference after 6 months in the VD group.

Some studies confirmed the importance of apelin level at the neonatal periods and its relationship with anthropometric indicators during the postpartum period because of the apelin-36 secretion in human breast milk.[26,27] And also production and increasing of the biologically active form of apelin and its mRNA during lactation in the mammary gland as well as its secretion in milk and colostrum has been proven by Habata et al. and Aydin *et al.* too.[26,27]

Furthermore, studies reported the important role of apelin in the control of energy metabolism and energy balance,[20,28] And its secretion in milk influences food intake, the regulation of growth in early infancy, and the development of metabolic disorders in childhood and adulthood.[20]

Further evidence about the important role of apelin in the postnatal period has been given by Wang et al. research. They showed the expression of apelin in rat stomachs during the fetal and postnatal periods was higher than in adult rats.[29] Accordingly, in addition, apelin concentration leads to the reduction of obesity because of an increase in energy consumption.[28] Based on the above studies, it seems that angiogenesis, cell proliferation, and hormonal changes that are mediated in the hypothalamus through CCK(Cholecystokinin) contribute to the relationship between apelin-36 and children's anthropometric indices.[28-30]

In addition, Than et al. (2012) confirmed the probable role of apelin in obesity and claimed that apelin autocrine signalling may be used as a new treatment objective for obesity and other metabolic diseases.[31] On the other hand, according to Pei et al. 2014, cesarean delivery could be considered a risk factor for obesity in early childhood;[32] as well, Pluymen et al. (2016) and some

other research reveal that children delivered by cesarean had an approximately 50% higher risk of being overweight throughout childhood compared with children delivered vaginally.[33-35]

Given the wide role of apelin in obesity and metabolic syndrome[10,20] as well as the importance of this hormone as a powerful angiogenic factor for normal vascular development and considering positive upregulation of this hormone by Sex-steroids, insulin, TNF-α (Tumor Necrosis-Factor Alpha) and growth hormone VD[16,18] as well as relationship investigated in our study, it can be concluded that this hormone can have a relation with children anthropometric indices.

CONCLUSIONS

Analysis in the present study shows that there was a close relationship between apelin-36 and infants' anthropometric indices in the VD group. This suggests the important role of apelin-36 in infant growth after 6 months years old. Given the potential role of apelin in modulating normal blood vessel growth, glucose homeostasis, and energy balance it seems apelin has a role in the development of a child. The different results in the two groups may be due to the different metabolic regulations as well as different serum apelin levels in CS and VD groups.

Although both group's children's feeding was homogenous, there is still a need to calculate the effect of micronutrients as well as maternal diet precisely in a future study. However, our study has its limitations such as the sample size was small, undoubtedly with a larger sample size as well as long- term follow up we could have better sight through the relations, and also considering the multiple time for measuring serum level of apelin-36 in mothers and infants besides cord blood sample are deemed necessary. It is likely that apelin-36 can be used in the future as a biomarker to predict infant growth. Thus, more studies are needed in the future.

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