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Effect of adrenocorticotropin hormone and cortisol on epithelial sodium channels according to delivery route

Adrenokortikotropin hormon ve kortizolün doğum şekline göre epitelyal sodyum kanalları üzerine etkisi

Gönül Tezel [1], Osman Öztekin [2], Salih Kalay [3], Mehmet Akdağ [4], Murat Turhan [4], Nuray Erin [5], Mustafa Akçakuş [3], Nihal Oygur [3]

[1] University of Health Science, Antalya Education and Research Hospital, Antalya, Turkey
[2] Tekden Hospital, Denizli, Turkey
[3] Akdeniz University, School of Medicine, Department of Pediatrics, Division of Neonatology, Antalya, Turkey
[4] Akdeniz University, School of Medicine, Department of Otolaryngology, Antalya, Turkey
[5] Akdeniz University, School of Medicine, Department of Pharmacology, Antalya, Turkey

ORCID ID of the author(s)
GT: 0000-0002-1054-535X
OÖ: 0000-0002-1150-2175
SK: 0000-0003-4230-7708
MA: 0000-0003-1377-4227
MT: 0000-0001-6140-1666
NE: 0000-0002-6116-1970
MA: 0000-0001-8007-797X
NO: 0000-0001-8790-6136

Corresponding author / Sorumlu yazar:
Gönül Tezel
Address / Adres: Sağlık Bilimleri Üniversitesi, Neonatoloji Anabilim Dalı, Antalya, Türkiye
E-mail: tezelgonul@hotmail.com

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Abstract

Aim: Immaturity of epithelial sodium channels (ENaC), which are affected by adrenocorticotropin hormone (ACTH) and cortisol, is believed to be the major underlying cause of transient tachypnea of the newborn. The aim of this study is to investigate the differences in ACTH and cortisol levels and the expression of lung ENaC α subunit of the babies in relation to mode of delivery.

Methods: The study was planned as prospective cohort study. Eighteen women who underwent elective caesarean section (C/S) and fifteen women who admitted to hospital for normal spontaneous delivery (NSD) and their term 33 newborn infants were included in the study. Blood samples for ACTH and cortisol levels were collected from the mothers prior to birth and the newborn infants 1 hour after birth. Nasal mucosa species of the infants were performed to assess ENaC α subunit levels.

Results: The ACTH and cortisol levels of mothers of C/S group were lower than the ACTH and cortisol levels of mothers of NSD group ($p<0.001$). Although the ACTH levels of infants delivered by C/S were significantly higher than the ACTH levels of infants delivered by NSD ($p=0.001$), no significant difference was identified between them with regards to the levels of cortisol ($p=0.078$) and ENaC α subunits ($p=0.671$).

Conclusion: Our results suggest that hormonal mechanisms in newborn infants function independently from their mothers. In term babies mode of delivery is not the major factor affecting the expression of ENaC α subunit.

Keywords: Adrenocorticotropin hormone, Cortisol, Epithelial sodium channels, Delivery route

Öz

Amaç: Adrenokortikotropin hormon ACTH ve kortizolün etkilediği epitelyal sodium kanalı (ENAC) immatüritesinin Yenidoğanın takipnesinin altta yatan başlıca nedeni olduğuna inanılmaktadır. Bu çalışmanın amacı doğum şekline göre ACTH, kortizol düzeylerinin ve bebeklerin akciğer ENaC alfa subünit ekspresyonunun ilişkisinin araştırılmasıdır.

Yöntemler: Çalışmamız prospektif kohort çalışma olarak planlandı. Hastanemizde elektif sezaryen(C/S) planlanan 18 gebe ve normal spontan doğum (NSD) için başvuran 15 gebe ve onların miat 33 yenidoğan bebekleri çalışmaya dahil edildi. ACTH ve kortizol için kan örnekleri annelerden doğumdan önce ve bebeklerinden doğumdan 1 saat sonra alındı. Bebeklerin ENaC α subunit değerlendirmesi için burun mukoza örnekleri alındı.

Bulgular: Sezaryen olan annelerin ACTH ve kortizol düzeyleri NSD yapan annelerin ACTH ve kortizol düzeylerinde daha düşüktü ($p<0,001$). Sezaryen ile doğan bebeklerin ACTH düzeyleri NSD ile doğan bebeklerin ACTH düzeylerinden anlamlı derecede yüksek ($p<0,001$) olmasına rağmen kortizol ($p=0,078$) ve ENaC α subunit düzeyleri arasında fark saptanmadı ($p=0,671$).

Sonuç: Çalışmamızın sonuçları yenidoğan bebeklerde hormonal mekanizmaların annelerinden bağımsız olduğunu göstermektedir. Miat bebeklerde doğum şeklinin ENaC α subünit ekspresyonunu etkileyen ana faktör olmadığını göstermektedir.

Anahtar kelimeler: Adrenokortikotropin hormon, Kortizol, Epitelyal sodium kanalı, Doğum yolu

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Introduction

It is believed that the underlying cause of transient tachypnea of the newborn is the lack of maturation of epithelial sodium channels (ENaC), which play an important role in controlling sodium movements and in the absorption of fluids in the alveoli [1-3]. ENaC in the airway epithelium is constituted of 3 sub units, which are α, β and γ. The α subunit is responsible for the channel functions of ENaC [4].

During pregnancy, the release of CRH (corticotrophin releasing hormone) from placental and fetal membranes increases progressively. By increasing both fetal adrenocorticotropin hormone (ACTH) and adrenal gland cortisol release, placental CRH initiates the process of delivery and enables the maturation of the fetus lung for postnatal adaptation [5]. As this mechanism is not involved in elective caesarean section, sufficient lung maturation and fetal lung fluid reabsorption does not take place. This factor along with iatrogenic prematurity contributes to a greater frequency of respiratory morbidity. Furthermore, it is known that these respiratory diseases' progression is also different in elective caesarean sections performed prior to the initiation of the delivery process, that these newborn infants require oxygen for longer periods, and that there is an increased need for CPAP and mechanical ventilation for these newborn infants [6]. It has been clinically demonstrated that the administration of antenatal corticosteroids in pregnant women with elective caesarean section planned in or near their term increases the clearance of fluids in the lung of their newborn [7].

The aim of this study is to evaluate the effects of ACTH and cortisol levels on the expression of neonate lung ENaC α subunit in mothers giving birth by spontaneous delivery and caesarean section delivery and their newborn infants. The study also aims to investigate the changes observed in hormone release according to the method of delivery.

Materials and methods

The study was planned as prospective cohort study. Eighteen pregnant women giving birth by elective caesarean section delivery and fifteen normal spontaneous vaginal delivery were included into this study along with their 33 newborn infants between January 2011 - September 2011 at the Akdeniz University Medical Faculty, Department of Gynecology and Obstetrics. Approval from the Akdeniz University Medical Faculty Ethics Committee was obtained prior to the study commencement (Ethics Committee approval no.: B.30.2.AKD.0.20.05.05/249). For pregnant women participating to the study, consent for blood sampling was also obtained.

Pregnant women with the prenatal risk factors of hypertension, eclampsia, early membrane rupture, diabetes or symptoms of infection were excluded from the study. Newborn infants born prior to 37 weeks of gestation, with perinatal asphyxia, or with meconium aspiration syndrome were also excluded from the study, as were the newborn of mothers who received antenatal steroids. In addition, cases which underwent urgent caesarean section for various reasons, such as fetal distress or labor in which normal spontaneous delivery commenced but did continue, were also not included into the study.

Pregnant women

From the eighteen mothers who have completed thirty seven weeks of gestation and underwent elective caesarean section, blood samples for ACTH and cortisol tests were obtained before epidural and/or general anesthesia was performed. From fifteen pregnant women admitted to hospital for normal spontaneous vaginal delivery (NSD), blood samples were obtained for ACTH and cortisol tests when their cervical opening was 4-6 cm and before spinal anesthesia was performed.

Newborn infants

Postnatal routine care and examinations were performed on the 33 newborn of mothers who gave birth by elective caesarean section or normal vaginal delivery. Twelve of the children were males (36.3 %) and twenty one were females (63.7 %). The newborn infants were also weighted. Their weight, gender, hour of birth, whether they had respiratory problems and whether they need intensive care was recorded. Their arterial blood pressure was measured in the first hour, before the blood samples were taken. One hour after birth, blood samples for ACTH and cortisol were obtained, and nasal mucosa sample from the frontal 1/3rd section of the nasal septum was collected with a rhinoprobe (Martin, Germany) in order to determine ENaC α subunit mRNA expression.

Clinical chemistry tests

Venous blood was collected for clinical chemistry assessments. Blood sugar was determined from the venous blood for each patient by using glucometer (GlucoLeader Yasee, LOTHA no 17082).

Blood samples for ACTH measurement were collected in tubes with EDTA and shipped in ice, while blood samples for cortisol measurement were collected in tubes without anticoagulants and shipped at room temperature to the laboratory. Plasma and serum in the samples were separated by centrifuging for 15 minutes. The separated plasma and serum were kept at -80°C until the assessment were performed.

Measurement of serum cortisol

By using the electrochemiluminescence immunoassay (ECLIA) procedure (Roche Modular Analytics E170), serum samples were measured in the immunoassay analyzer. The kit's intra-assay CV was 1.1% (control value: 15.1 µg/dL), inter-assay CV was %1.7 (control value: 14.8 µg/dL)

Serum ACTH measurement

Plasma samples with EDTA were measured by using the ECLIA procedure with the Cobas e 602 immunoassay analyzer within the Cobas 8000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The kit's intra-assay CV was %1.5 (control value: 115 pg/mL), inter-assay CV was %1.7 (control value: 115 pg/mL) and the minimum level of insulin that could be measured was 1.0 pg/mL.

Quantification of the α-ENaC subunit mRNA in the nasal mucosa sample of newborn infants

The nasal mucosa samples obtained from the newborn infants were kept in RNAlater solution (RNA Stabilization Reagent for stabilization of RNA; QIAGEN Cat. No. 76104) at -20ºC until RNA isolation was to be performed. Approval from the Akdeniz University Medical Faculty Ethics Committee was

obtained prior to the procedure. (Ethics Committee approval no.: B.30.2.AKD.0.20.05.05/249)

Once all samples were collected, RNA was extracted by using High Pure RNA Isolation Kit (Roche Cat. No. 11 828 665 001). The qualitative and quantitative analysis of the obtained RNA samples was performed by a spectrophotometer (Beckman Coulter DU Series 700 Spectrophotometers Item No. A49421). A certain quantity of RNA was separated to prepare cDNA, and the remaining RNA samples were kept at -80ºC.

To obtain cDNA from RNA, Transcriptor High Fidelity cDNA Synthesis Kit (Roche Cat. No.05 081 955 001) was used. To test the cDNA that was obtained, PCR was performed using GADPH primers according to the procedure recommended by the kit. The results were controlled in 2% agarose gel.

After the PCR result was obtained, RealTime-PCR (RT-PCR) was performed for the α-ENaC subunit. The obtained results were quantified in proportion to the GAPDH gene.

RT-PCR protocol (LC480)

The solutions to be used (water, probes master, primer) were removed from -20°C storage and thawed. Prior to opening their lids, samples were centrifuged in a microcentrifuge. Solutions were kept in ice during this procedure. The solution mixes were prepared according to the number of samples. The mixes were stirred with the use of a pipette. Of this mix, 8 µl were added to each cuvette of the LightCycler 480 Multiwell Plate. Following this, 2 µl of cDNA was added to each cuvette. Plate Lightcycler 480 was closed using the Sealing Foil (Lightcycler 480 Sealing Foil: Cat. No. 04 729 757 001). The Plate was centrifuged at 1500g for 2 minutes. LightCycler 480 (LightCycler 480 Instrument: Cat. No. 05 015 278 001) was placed in its device, and measurements were performed according to the protocol recommended by the kit (LightCycler 480 Probes Master: Cat. No. 04 707 494 001 and Real Time ready Assay: Cat. No. 05 532 957 001).

Statistical analysis

The data were analyzed using SPSS (version 20). To define the sample, statistics such as the frequency distribution, mean, standard deviation and median were used. In the comparison of continuous variables based on groups, the difference test between two means according to distribution assumptions or the Mann-Whitney U test were employed. The relation between continuous variables was assessed using the Spearmen Correlation analysis. In addition, the Chi-squared test was employed in the analysis of categorical variables. To be able to identify differences in the analysis, a 95% level of significance was used.

Results

Eighteen pregnant women giving birth by elective C/S (54.5% of cases) and fifteen pregnant women giving birth by NSD (45.5% of cases) were included into this study along with their newborn infants between January 2011 - September 2011 at the Akdeniz University Medical Faculty Department of Gynecology and Obstetrics. Informed consent was obtained from all pregnant women. Spinal anesthesia was used in all 18 (100%) of the mothers giving birth by elective C/S and in 1 (6.6%) of the mothers giving birth by NSD. TTN developed in 2 (11.1%) of the newborn infants delivered by elective C/S and in 1 (6.6%) of the newborn infants delivered by NSD. Oxygen support was provided to these newborn infants.

Evaluation of the data for the mothers

ACTH levels in mothers giving birth by elective C/S [39.89 pg/mL [7.90-96.13] were found to be significantly lower compared to the levels in mothers giving birth by NSD [118.80 pg/mL [30.90-354] (p<0.001). Similarly, cortisol levels in mothers giving birth by elective C/S [31.28 µg/dL [17.41-48.97] were found to be significantly lower compared to the levels in mothers giving birth by NSD [52.68 µg/dL (25.33-138.30)] (p<0.001) (Table 1).

Evaluation of the data for the newborn infants

Of the infants born by elective C/S, 5 were male (27.8%) and 13 were female (72.2%), while of the infants born by NSD, 7 were male (46.7%) and 8 were female (53.3%).

Gestation age was determined as 38 weeks (38-39) for infants born by elective C/S and 39 weeks (38-40) for infants born by NSD. A statistically significant difference was identified between these two groups (p=0.001). Of the infants born by elective C/S, 13 (72.2%) were delivered in 38th week of gestation, and 5 (27.8%) were delivered in the 39th week of gestation or later; of the infants born by NSD, 3 (20%) were delivered in the 38th week of gestation, and 12 (80%) in the 39th week of gestation or later. The birth weight of the infants delivered by elective C/S was determined as 3200 gr (2568-4150), and for the infants delivered by NSD it was determined as 3305 gr (2735-3790). No statistically significant difference was identified between these two groups (Table 2).

ACTH levels of infants born by elective C/S [141.4 pg/mL (19.39-447.40)] were found to be significantly higher (p=0.001) than the ACTH levels of infants born by NSD [47.56 pg/mL (15.64-119.70)]. On the other hand, no significant difference was identified (p=0.078) between the levels of cortisol of infants born by elective C/S [20.56 µg/dL (8.67-33.85)] and the levels of cortisol for infants born by NSD [27.56 µg/dL (6.97-48.75)].

Table 1: Comparison of laboratory data according to method of delivery

Parameters Evaluated	Method of Birth	Median (Minimum-Maximum)	p
ACTH (pg/mL)	C/S* (n:18)	39.89 (7.90-96.13)	<0.001
	NSD** (n:15)	118.80 (30.90-354)	
Cortisol (µg/dL)	C/S (n:18)	31.28 (17.41-48.97)	<0.001
	NSD (n:15)	52.68 (25.33-138.30)	

* Mother giving birth by caesarean section, ** Mother giving birth by normal spontaneous vaginal birth

Table 2: General data for newborn infants born by C/S and by NSD

General Characteristics	Group	Number of Cases	Median (Minimum-Maximum)	p
Gestation Week	C/S*	18	38.2 (38-39)	0.001
	NSD**	15	39 (38-40)	
Birth Weight (gram)	C/S	18	3200 (2568-4150)	0.874
	NSD	15	3305 (2735-3790)	
Blood Sugar (mg/dL)	C/S	18	76.50 (56-111)	0.856
	NSD	15	79.00 (59-11)	
Systolic Blood Pressure (mmHg)	C/S	18	69.50 (57-81)	0.542
	NSD	15	69.00 (53-103)	
Diastolic Blood Pressure (mmHg)	C/S	18	38.00 (23-59)	0.741
	NSD	15	34.00 (21-60)	

* Newborn infants born by caesarean section, **Newborn infants born by normal spontaneous vaginal delivery

The ENaC α subunit level in newborn infants delivered by elective C/S was determined as 2.729 relative to the expression of GADPH (1.0-4.98), and for newborn infants

delivered by NSD it was determined as 3.39 relative to the expression of GADPH (0.445-5.769). No statistically significant difference was identified between the two groups (p=0.671) (Table 3, 4).

Evaluation of the data for the newborn according to the gestation periods

When the data of the newborn infants were evaluated according to their gestation ages, it was determined that the birth weight of infants born in the 38th week was 2990 gr (2568-4150), while the birth weight of infants born in the 39th week or later was 3390 gr (3015-3900). No statistically significant difference was identified between the two groups based on their birth weight according to gestation weeks (p=0.671) (Table 3, 4).

Similarly, no statistically significant difference was identified (p=0.140) between the ACTH levels for infants born in the 38th week [114.2 pg/mL (19.39-447.40)] and the ACTH levels for infants born in the 39th week or later [59.47 pg/mL (15.64-209.50)].

Table 3: ACTH, cortisol and ENaC α subunit levels for newborn infants

Parameters Evaluated	Method of Delivery	Median (minimum-maximum)	p
ACTH (pg/mL)	C/S* (n:18)	141.40 (19.39-447.40)	0.001
	NSD** (n:15)	47.56 (15.64-119.70)	
Cortisol (µg/dL)	C/S (n:18)	20.56 (8.67-33.85)	0.078
	NSD (n:15)	27.56 6.97-48.75	
ENaC α subunit	C/S (n:18)	2.729 (1.0-4.98)	0.671
	NSD (n:15)	3.39 (0.445-5.76)	

* Newborn infants born by caesarean section, * Newborn infants born by spontaneous vaginal delivery

Table 4: Comparison of the ACTH, cortisol and ENaC α subunit levels according to gestation age of newborn infants

Evaluated Parameters	Infants born in 38th week of gestation (n:16) Median (Minimum-Maximum)	Infants born in 39th week of gestation or later (n:16) Median (Minimum-Maximum)	p
ACTH (pg/mL)	114.2 (19.39-447.40)	59.47 (15.64-209.50)	0.140
Cortisol (µg/dL)	20.48 (8.67-48.75)	27.48 (6.97-39.52)	0.293
ENaC α subunit	2.955 (1.0-5.76)	2.675 (0.445-4.79)	0.295

With regards to cortisol, no statistically significant difference was identified (p=0293) between the levels for infants born in the 38th week [20.48 µg/dL (8.67-48.75)] and the levels for infants born in the 39th week of gestation or later [59.47 pg/mL (15.64-209.50)].

The ENaC α subunit level in newborn infants delivered in the 38th week was determined as 2.955 relative to the expression of GADPH (1.0-5.76), and for newborn infants delivered in the 39th week or later it was determined as 2.675 relative to the expression of GADPH (0.445-5.769). No statistically significant difference could be identified between the gestation period for the newborn infants and the ENaC α subunit levels (p=0.295).

Discussion

As is also the case worldwide, the frequency of elective caesarean section has risen significantly in our country over the last years based on the expectation that it will decrease the risk birth asphyxia, trauma and meconium aspiration encountered during delivery. However, as this method of delivery is often performed in the 37-38th weeks of gestation, which are accepted as being close to the end of term, infants are born before lung maturation is complete and transient tachypnea of newborn (TTN) is becoming an increasingly more frequent respiratory problem. It has been shown in the literature that elective caesarean section deliveries lead to iatrogenic prematurity, which causes an increase in respiratory morbidity in association with the insufficiency of surfactant production and TTN [8,9]. For this reason, ACOG and the European RDS have decided that elective caesarean sections should not be performed before the end of the 38th week of gestation as long as there are no problems necessitating an early delivery [10,11]. Taking this recommendation into consideration, efforts are now being made in our hospital's Obstetrics Clinic to avoid performing elective caesarean section prior to the 38th week of gestation. Despite these efforts, it was nevertheless found that the gestation week of infants born by elective C/S was significantly lower than the gestation week of infants born by NSD.

The process of delivery leads to a stress response by stimulating both the fetal and maternal systems. While pain, uterine contractions and the mother's anxiety during delivery stimulates stress hormones in the mother, the mechanical stress and hypoxia, associated with the infant's passage through the birth canal constitutes the fetal stress response. The stress experienced during the passage through the birth canal is essential for the adaptation of the newborn infant to postnatal life, and this stress stimulates stress hormones such as cortisol in infants born through NSD. It has been demonstrated in various studies that uterine contractions, pain and stress of delivery in the mother initiates this cycle during normal delivery and that, for this reason, ACTH levels are higher in mothers giving birth by NSD [12,13]. It was found in our study that ACTH levels were also significantly higher in mothers giving birth by NSD compared to the levels in mothers giving birth by caesarean section. Similarly, the level of cortisol in mothers giving birth by NSD was significantly higher compared to the levels in mothers giving birth by caesarean section.

It is known that during delivery, placental CRH increases cortisol release from the adrenal in the fetus by stimulating fetal ACTH secretion. For this reason, it is assumed that both the ACTH and the cortisol levels are higher in newborn infants that undergo normal spontaneous vaginal delivery and experience this trauma. However, contrary to what might be expected, our study's results have shown that ACTH levels in infants born by NSD is lower compared to the ACTH levels observed in infants born by caesarean section. Although no statistically significant difference was identified between the two groups of newborn infants with regards to the levels of cortisol, the level of cortisol in infants born by NSD was found to be slightly higher in comparison to the level of cortisol in infants born by caesarean section. Several differences are observed in the results of studies conducted on ACTH and cortisol level in newborn infants depending on the method of delivery [14-17]. In Ocheldalski's study [13], no difference was identified in the umbilical cord ACTH levels in infants born by caesarean section and NSD. On the other hand Zenciroğlu et al. [14] determined that while umbilical cord ACTH levels were higher in newborn infants born by NSD, no difference was found in the 1st hour venous blood samples.

In our study, depending on the method of delivery, both the ACTH and cortisol levels of mothers giving birth by NSD was higher than the ACTH and cortisol levels observed in mothers giving birth by caesarean section. On the other hand, ACTH levels in infants born by NSD were found to be lower compared to the levels in infants born by caesarean section, while the cortisol level in both groups was determined to be close to one another. These results appear to indicate that it is necessary for a certain level of cortisol to be attained by the newborn for postnatal life, and that in order to achieve this, the newborn infant can modify its own levels of ACTH, regardless of the method of delivery or maternal influence. In addition, the independence of the newborn infant's ACTH and cortisol levels from their mother suggest that the underlying causes of fetal and maternal stress might be different.

The higher frequency of TTN in infants that are born by elective caesarean section has led to an increase in the number of studies conducted on the endogenous factors that are involved in the regulation of ENaC expression during delivery. Our results demonstrate that ENaC α subunit expression does not vary according to the method of delivery or gestation week (p: 0.671 according to the method of delivery, and p: 0.295 according to gestation week). We are of the opinion that the lack of difference in the level of expression of ENaC α subunit between the two groups is due to the importance of the role of cortisol in ENaC expression and the fact that cortisol levels in both groups of newborn infants were very close to one another. The results regarding the relation between ENaC subunit expression and the method of delivery in the previously conducted studies are also contradictory. Baines et al. [18] have concluded that day 1 ENaC α subunit expression in newborn guinea pigs undergoing term C/S delivery is higher than in term normal newborn infants born by vaginal delivery, and that ENaC α subunit expression is independent of the process of delivery and that expression increases postnatally. In their study, Helve et al. [19] have assessed postnatal ENaC α subunit expression at 1-5 hours and 22-28 hours after birth in term newborn infants, and determined that there were no differences based on method of delivery at 1-5 hours. However, while the ENaC α subunit expression of infants born by term vaginal delivery decreased at 22-28 hours, this decrease was not observed in infants born by caesarean section. The high level of ENaC α subunit level observed for a longer period in infants born by caesarean section was explained by the fluid absorption potential being possibly higher in infants born by vaginal delivery. In the study conducted by Janer et al. [20], while ENaC α subunit expression in the first 3 hours was higher in infants born by elective caesarean section than in infants born by vaginal delivery, no difference in levels of expression was identified at the 24th and 48th hours after birth. While the gestation week of the newborn from both groups in the study of Helve et al. [19] were similar, the gestation weeks of newborn infants born by caesarean section was found to be lower, which was also the case in our study. In Janer et al.'s study [20], a positive correlation was identified between the ENaC α subunit expression in nasal mucosa collected in the first 30 minutes following caesarean section delivery and the plasma cortisol in the umbilical cord blood, and when all cases included to the study were evaluated together, saliva cortisol and ENaC α subunit mRNA expression were also found to be correlated in the first 2 hours after birth. In our study, no correlation was identified between the ACTH and cortisol levels and the levels of ENaC α subunit in infants born by either elective caesarean section or NSD.

The limitation of our study is that the number of cases is low and the blood is taken in a single hour for hormone levels which is a dynamic process.

In conclusion, our study's results have demonstrated that although ACTH and cortisol levels in mothers giving birth by NSD is higher than the ACTH and cortisol levels in mothers giving birth by caesarean section, the levels observed in the infants are not in accord with the values observed in their mothers. In parallel with the cortisol levels in the newborn infants, no differences were identified between the groups with regards to ENaC α subunit expression. Our results suggest that hormonal mechanisms in newborn infants function independently of their mothers, and that infants might regulate their own ACTH levels in order to maintain their cortisol level at a certain level. However, as the ACTH and cortisol hormones that were assessed are very dynamic substances, capable of significantly changing within a few hours, we consider that it might be beneficial to assess ACTH, cortisol levels and ENaC α subunit expression at birth and also 1, 2, 6, 12, 24, 36 and 48 hours after birth, in order to clarify the relationship between them more apparent.

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