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The correlation of maternal serum and cord blood copeptin levels with intrapartum fetal distress

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Summary

Aim: Fetal distress (FD) is mostly an important sign of fetal hypoxia. The hypothalamic-pituitary-adrenal axis is an important limb of acute stress response. Copeptin is a hormone of endogenous stress. The authors aimed to investigate whether the level of copeptin correlates with FD or not. *Material and Methods:*Twenty-four pregnant women and their babies with the diagnosis of FD confirmed by category III fetal heart rate (FHR) pattern were compared with 20 uncomplicated pregnant women and their babies who were delivered by elective cesarean section. *Results:* The mean maternal serum copeptin level showed no significant difference between the mothers of control group and the mothers of FD group ($p > 0.05$). The mean umbilical cord serum copeptin level showed no significant difference between the groups ($p > 0.05$). *Conclusion:* The authors revealed that copeptin is not correlated with the presence of FD, thus further studies are needed to discover new biomarkers.

Key words: Biomarker; Copeptin; Fetal distress; Vasopressin.

Introduction

Fetal distress (FD), one of the most important reason causing perinatal mortality and neonatal morbidity, signifies that the fetus' health is threatened because of acidosis and hypoxia [1]. Detection of FD plays an important role in intrapartum surveillance. Electronic fetal heart rate (FHR) monitoring is important for the clinician to realize the development of hypoxia [2, 3].

It is accepted that the progression of FHR tracing to the category III (abnormal) pattern strongly predicts FD according to the American Congress of Obstetricians and Gynecologists intrapartum FHR trace management protocol. Although FHR tracing is a method with high sensitivity especially in acidemic fetuses, its specificity is low [4-6]. It is better to justify the diagnosis of FD with a fetal blood acid base measurement. The need of markers that may be valuable for detecting the true FD arises.

In this study, the authors compared maternal serum and fetal cord blood copeptin levels between pregnant women with and without FD confirmed by category III FHR pattern and raised the question whether maternal serum and fetal cord blood copeptin levels are associated with the presence of fetal FD.

Materials and Methods

This prospective study was carried out between July and September 2015 at Gynecology and Obstetrics Service of Medical Sciences University Istanbul Ümraniye Medical and Research Hospital which is a tertiary care centre in Istanbul, Turkey. Written informed consents were taken from all participants which were between 34 and 42 weeks of gestation and presenting for delivery during this period. The study was approved by the ethics committee of Medical Sciences University Istanbul Ümraniye Medical and Research Hospital. Gestational age was determined on the basis of the first day of mother's last menstrual period and an early ultrasound scan in the first trimester.

The subjects were divided into two groups, as study and control groups, according to the FD presence. FD was determined by using fetal monitoring based on the American Congress of Obstetricians and Gynecologists intrapartum FHR trace management protocol [7]. Cesarean section decision was made by the same authors (İ.U. and Y.Ç.). According to the mentioned management protocol, category II (intermediate) cases were evaluated and under surveillance and if the FHR tracing progressed to a category III (abnormal) pattern, then delivery was considered. General anesthesia was administered in all participants.

Multi fetal gestations, pregnants with hypertension, preeclampsia, eclampsia, diabetes mellitus, chronic diseases, and fetuses with congenital malformations were excluded from the study.

Birth weight, first minute Apgar score, fifth minute Apgar score, and umbilical artery pH were obtained and recorded for all participants.Five ml of maternal venous bloods were taken before the cesarean section and three ml of cord bloods from fetal side of the umbilical cords were drawn immediately after delivery of the fetuses. All samples were collected in a vaccutainer tube, and then the serum was separated, collected and stored. After centrifugation, serums were frozen in sterile tubes at -20°C until the time of assay. Maternal and cord blood serum copeptin levels were measured with enzyme-linked Immunosorbant assay (ELISA) by according to the methods recommended by the manufacturer. The groups were compared regarding maternal serum and fetal cord blood copeptin levels and recorded data.

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Table 1. — *Clinical descriptive data of the groups*.

	Control (n=20) Mean ± SD	FD (n=24) Mean ± SD	Total (n=44) Mean ± SD	*p*
Maternal age (years)	29.5 ± 4.93	27.29 ± 6.02	28.3 ± 5.6	[1]0.196
Gestation at delivery	38.99 ± 1.18	38.87 ± 1.81	38.92 ± 1.54	[1]0.806
Sex of the babies, n (%)				
Females	8 (40%)	10 (41.7%)	18 (40.9%)	[2]1.000
Males	12 (60%)	14 (58.3%)	26 (59.1%)	
Neonatal birth weight (grams)	3,454.75 ± 418.69	3,178.96 ± 501.81	3,304.32 ± 481.09	[1]0.057
Neonatal height (cm)	51.12 ± 2.42	49.83 ± 2.1	50.37 ± 2.3	[1]0.078
1st minute apgar score	8.4 ± 0.75	7.75 ± 1.42	8.05 ± 1.2	[3]0.130
5th minute apgar score	9.7 ± 0.66	9.08 ± 1.02	9.36 ± 0.92	[3]0.021*
Intensive care unit, n (%)	0 (0%)	3 (12.5%)	3 (6.8%)	[2]0.239
Multiparity, n (%)	15 (75%)	7 (29.2%)	22 (50%)	[2]0.006**
Nulliparity, n (%)	5 (25%)	17 (70.8%)	22 (50%)	[2]0.006**

*[1]Student t-test, [2]Continuity (Yates) Correction, and Fisher's Exact test were used, [3]Mann Whitney U Test, *p < 0.05, **p < 0.01.*

Table 2. — *Comparison of the maternal serum copeptin levels between the groups.*

	Maternal copeptin (ng/dl) Mean ± SD
Control	927.75 ± 80.33
FD	950.25 ± 197.25
Total	940.02 ± 154.24
p	0.572

Mann Whitney U Test

Table 3. — *Comparison of the umbilical cord serum copeptin levels between the groups.*

	Umbilical cord serum copeptin (ng/dl) Mean ± SD
Control	800.35 ± 438.03
FD	875.75 ± 141.02
Total	841.48 ± 311.22
p	0.860

Mann Whitney U Test

Datas were expressed as mean ± SD. Differences in the means of variables were tested using both parametric (Students-*t* test) and non-parametric test (Mann-Whitney-U test) depending on the distribution of the variables. Correlation analyses were conducted using Spearman or Pearson correlation coefficients depending once again on the distribution of the variables. A probability value of less than 0.05 was considered significant. SPSS version 10.1 was used for analysis. Post-hoc power analysis with the effect width in one degree of freedom (α=0.05 and β=0.20) Power Analysis Sample Size Software (PASS) was done by using test 19.

Results

A total of 44 women between the ages of 18 and 39 and their babies were included to the present study after 4 subjects (8.3 %) were excluded due to insufficient data. All women were between 34 and 42 weeks of gestation.Twenty four pregnant women and their babies with the diagnosis of FD according to FHR trace management protocol were compared with 20 normal uncomplicated pregnant women and their babies who were delivered by elective cesarean section.

The mean maternal age was 28.3±5.6 years and 40.9% of the babies (n=18) were female and 59.1% (n=26) were male. The mean maternal age showed no significant difference between control group and study group (29.5 ± 4.93 *vs.* 27.29 ± 6.02) ($p > 0.05$).

The mean gestational age at delivery and the mean of neonatal birth weights showed no statistically significant difference between the control and study groups (38.99 ± 1.18 *vs.* 38.87 ± 1.81), (3,454.75 ± 418.69 *vs.* 3,178.96 ± 501.81) ($p > 0.05$). The mean of heights (51.12 ± 2.42 *vs.* 49.83 ± 2.1) and distribution of sex of the babies [female: 8 (40%) *vs.* 10 (41.7%), male: 12 (60%) *vs.* 14 (58.3%)] ($p > 0.05$) were not found statistically different between the control and the study groups. (Table 1).

The fifth minute Apgar scores in the control group babies were significantly higher than in FD group (9.7 ± 0.66 *vs.* 9.08 ± 1.02) ($p = 0.021$; $p < 0.05$), whereas the first minute Apgar scores showed no significant difference between the groups (8.4 ± 0.75 *vs.* 7.75 ± 1.42) (> 0.05). (Table 1)

The need of intensive care unit revealed no significant difference between the control and study groups (0 (%0) vs 3 (%12,5)) (p>0.05) (Table 1).

The ratio of multiparity was significantly higher in mothers of control group than the mothers of FD group [15 (75%) *vs.* 7 (29.2%)] ($p = 0.006$; $p < 0.01$), whereas nulliparity was significantly lower than the mothers of FD group [5 (25%) *vs.* 17 (70.8%)] ($p = 0.006$; $p < 0.01$) (Table 1).

The mean maternal serum copeptin level showed no significant difference between the control and the study groups (927.75 ± 80.33 *vs.* 950.25 ± 197.25) (p>0.05) (Table 2).

Table 4. — *The correlation between umbilical cord serum copeptin levels and the following variables: birth weight, first minute and fifth minute Apgar scores, umbilical artery pH, and maternal copeptin levels in the FD group.*

FD Group		Umbilical cord Copeptin (ng/dl)
Birth weight (grams)	*r*	0.092
	p	0.669
1st minute apgar score	*r*	0.014
	p	0.950
5th minute apgar score	*r*	-0.154
	p	0.473
Umbilical artery pH	*r*	0.008
	p	0.969
Maternal copeptin (ng/dl)	*r*	0.729
	p	0.001**

***p* < 0.01*

The mean umbilical cord serum copeptin level showed no significant difference between the control and the study groups (800.35 ± 438.03 *vs.* 875.75 ± 141.02) ($p > 0.05$) (Table 3).

Umbilical cord serum copeptin levels showed no significant correlation with birth weights, and first and fifth minute Apgar scores, umbilical artery pH ($p > 0.05$).
There was a significant positive correlation (72.9%) between umbilical cord serum copeptin levels and maternal serum copeptin levels ($p = 0.001$; $p < 0.01$) (Table 4).

Discussion

This prospective study aimed to investigate whether the level of maternal serum and fetal cord blood copeptin correlated with the presence of FD or not. Any significant difference could not been found between the groups in terms of maternal serum and fetal cord blood copeptin levels.

Although a non-invasive measure of fetal hypoxia would be useful, yet we are not aware of any known maternal biomarker of fetal hypoxia. Myers *et al.* reported that arginin vasopressin (AVP) is a hormone produced by hypothalamus in fetal hypoxia [8]. Copeptin is a precursor of preprovasopressin which is secreted in an equimolar ratio to AVP in situations of high plasma osmolality, low blood pressure, and hypoxia [9]. Copeptin is selected as a marker of hypoxia in the present study because AVP is released in a pulsatile pattern with a half-life of 4-20 minutes and it is not possible to detect its concentration correctly [10].

According to the results of the present study, maternal serum copeptin levels showed no significant difference between the groups despite the significant positive correlation between umbilical cord and maternal serum copeptin levels. Contrary to the results of this study, Schlapbach *et al.* reported that neonates with perinatal asphyxia had higher copeptin cord blood concentration due to possible brain damage [11]. They showed that cord blood copeptin levels were inversely correlated with umbilical artery pH and suggested that the AVP response in neonates was activated due to perinatal stress.

It is also reported in the literature that copeptin concentrations in umbilical cord blood is higher after vaginal delivery than cesarean section [12]. The authors also concluded that vaginal birth is undoubtedly the most intense stressor in life. In the present study the authors included only women given birth via cesarean section. This may be a reason of the present lower copeptin levels in FD unlike previous studies reported higher copeptin levels [13].

Small sample size seems a limitation of this study however the minimum sample size was calculated as 20 patients in both groups according to the post-hoc power analysis. However also further studies with larger sample sizes may confirm the present results. Comparison of fetal pH values and maternal and cord blood copeptin levels can be designed as a new study regarding this issue.

Conclusion

As a conclusion the authors report that maternal serum and fetal cord blood copeptin are not a reliable marker for detection of FD, thus further studies are needed to discover new biomarkers.

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