Serum Copeptin Level as A Diagnostic and Prognostic Marker in Threatened Preterm Labor

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Abstract

Background: Copeptin is a stable by-product of the synthesis of arginine-vasopressin (AVP); it can be accurately and quantitatively measured in plasma and mimics the release of AVP.

Aim of work: to assess the importance of maternal serum copeptin levels in diagnosis of threatened preterm labor and prediction of preterm birth.

Subjects & methods: This study was carried out as a prospective case control on 88 pregnant women at Obstetrics and Gynecology Department, Faculty of Medicine, Menoufia University. They were divided into two groups: Group I (Case group n=58): including 58 pregnant ladies who admitted for threatened preterm labor. Group II (Control group n=30): including 30 healthy pregnant ladies of matched age, parity, and gestational age.

Results: Serum copeptin was significantly higher in cases with preterm labor than term controls (641.29±167.87 pg/ml vs 192.67±71.16 pg/ml) respectively. Regarding the outcome serum copeptin was significantly higher in cases with preterm birth than cases with term birth (751.57±169.923 pg/ml vs 642±163pg/dl) respectively. The serum copeptin cutoff value is ≥ 380 pg/ml, the area under the curve is equal to 1.00, according to our ROC data. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

Conclusion: Maternal serum copeptin levels can serve as a valuable diagnostic and predictive marker in cases of threatened preterm labor and preterm birth.

Keywords: Serum Copeptin, Diagnostic and Prognostic Marker, Threatened Preterm Labor.

Introduction

Globally, preterm birth is the leading cause of perinatal mortality and morbidity. There is some chance of treating and preventing premature birth. To prevent needless expenses and adverse effects, a precise diagnosis and efficient treatment are crucial. Ensuring effective therapy may also help to lower perinatal morbidity or mortality (1).

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Merely 10% of the women diagnosed with premature labor give birth before their due date. Interventions aimed at improving neonatal outcomes are less successful when preterm delivery is identified in later stages of pregnancy and when it is difficult to distinguish between true and false labor. Predictive biomarkers that are precise and timely are therefore required (2).

Preterm labor is predicted using cervical length measurement. Only a small fraction of patients who are predisposed to premature labor may be distinguished using this method. Depending on the sample population's risk of preterm labor, cervical length measurement can predict preterm delivery with a sensitivity of 35–70% (3).

Copeptin is a dependable measure of arginine vasopressin (AVP) and an endogenous stress marker. Copeptin is actually a useful biomarker that is raised in a variety of stressful situations and is utilized to help distinguish between various cases of acute myocardial infarction (4).

During pregnancy, copeptin levels rise; in preeclamptic pregnancies, this rise is more pronounced than in normal pregnancies. Copeptin levels during the first trimester may also be a predictor of gestational diabetes and preeclampsia in the future (5; 6).

The purpose of this study was to assess the predictive value of maternal serum copeptin levels for preterm birth and the identification of impending preterm labor.

Patients and Methods

A case control study conducted on 88 pregnant women at obstetrics and gynecology department, Faculty of medicine, Menoufia University during the period from November 2022 to April 2023.

Sample size estimation:

Sample size was calculated using PASS 11.0 and according to the power analysis results, with a 95% confidence interval and 80% test power, a one-way analysis of variance analysis should include a minimum of 88 pregnant women (58 of whom have threatening preterm labor and 30 of whom are healthy).

Ethical consideration:

After clarifying the purpose of the study, all of the women who were part of it gave their written informed consent. The Menoufia Faculty of Medicine's Ethical Scientific Committee approved the study protocol (IRB: 11-2022OBSG20).

Eligibility criteria:

Study included all pregnant in the second and third trimester at 24-34 weeks of gestation. Pregnant women having any of these issues were not include from our study:

1. Hypertension and diabetes either pregestational or gestational, Premature rupture of membranes, cardiac disease, kidney illness, and multiple pregnancies.
2. Those for whom continuing the pregnancy to term posed a serious risk to the fetus or mother.
3. Mothers suffering serious illnesses like sepsis, infections, and myocardial infarction.

Patients grouping:

Study included 88 pregnant women classified into:

- **Group I (Case group)**: consisted of 58 pregnant ladies who were admitted for threatened preterm labor. We depended on painful uterine contractions and the existence of changes in the cervix for the diagnosis of preterm labor. Group I was further subdivided into: **Preterm birth** including cases who gave birth prematurely before 37 weeks gestation & **Term birth** including cases who delivered at or after 37 weeks gestation.
- **Group II (Control group)**: consisted of 30 healthy pregnant ladies matching cases in age, parity and gestational age.

Study progress and evaluation:

All pregnant women included in the study had a full history taken including personal history, past history, present history and obstetric history with emphasis on age, special habits of medical importance, medical illness, gravidity, parity, miscarriage and last menstrual period. This was along with detailed clinical examination including general examination e.g. vital signs and BMI and abdominal & local examination e.g. fundal height, fundal grip, lateral or umbilical grip, 1st &2nd pelvic grip, auscultation of fetal heart sound, assessment of the membrane, determining of the presenting part, sterile speculum examination and fetal biometric measurements. Obstetric ultrasound was done for all included pregnant women to asses cervical length, cervical dilatation, status of membranes, fetal biometric measures, CTG and doppler study. Also, they were subjected to routine laboratory investigations where cases were subjected to CBC, CRP, Urea, Creatinine, AST, ALT, coagulation profile and blood grouping while controls were subjected to CBC and blood grouping.

Blood samples for the specific marker:

The laboratory work was done at Menoufia University's Faculty of Medicine, at the Clinical Pathology Department. We used meticulous aseptic precautions and obtained 5 mL peripheral blood samples in sterile tubes from each of the study's participating women. The Human Copeptin ELISA Kit (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China) was used to measure the level of copeptin in the serum.

Statistical analysis

Data was gathered throughout history, clinical examination and laboratory investigations, and SPSS (statistical program for social science) version 25 (Armonk, NY: IBM Corp.) was used to code, input, and analyze outcome measures. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, the data was examined for normality. Two types of statistics were done:

Descriptive statistics: Depending on the type of data, mean ± SD was used to describe quantitative data while numbers and percentages were used to represent **qualitative data**.

Analytic statistics: When comparing two groups with quantitative variables that had a normal distribution, the **student t-test** was employed (for parametric data). When comparing two groups with quantitative variables that don't have normal distribution, **Mann-Whitney U Test** was employed (for non-parametric data). To examine the relationship and comparison between two qualitative variables, the **chi-square test ($\chi 2$)** was employed. **Spearman's Correlation** was used for studying correlation. Receiver operating characteristic (ROC) curves were created to evaluate the parameters' clinical performance. For two-tailed tests, a **P-value** of less than 0.05 was considered significant statistically, while less than 0.001 indicated a very significant outcome.

Results

Table (1): Comparison between study group and control group regarding cervical length and dilatation:

	Cases group (n=58)	Control group (n=30)	t	P-value
Cervical length(mm) (Min. – Max.) Mean ± SD.	11.00 - 50.00 32.47 ± 8.19	30.00 - 52.00 42.77 ± 5.88	9.757	0.001**

Cervical dilatation(cm) (Min. – Max.) Mean ± SD.	1.00 - 6.00 2.26 ± 1.26	0.00 - 0.00 0.00 ± 0.00	-6.682	0.001**

t: Independent Samples t Test
p: p value for comparing between the studied groups
**: Highly significant, *: significant

This table shows us that the cervical length mean in cases group was 32.47±9.04 mm and ranged from 11 to 50 mm, and in controls it was 42.77±5.88 mm ranging from 30 to 52 mm which was significantly higher in controls than cases. In the other hand, cervical dilatation mean in cases was 2.26±1.26 cm, and the range was from 1 to 6 cm, and in controls it was zero, cervical dilatation was significantly higher in cases than controls.

Table (2): Comparison between study group and control group regarding Serum Copeptin:

	Cases group (n=58)	**Control group (n=30)**	**U**	**P-value**
Serum Copeptin(pg/ml) (Min. – Max.) Mean ± SD.	350.00 - 950.00 641.29 ± 167.87	110.00 - 350.00 192.67 ± 71.16	0.500	0.001**

U: Mann-Whitney U test, p: p value for comparing between the studied groups
**: Highly significant, *: significant

Serum Copeptin mean was 641.29±167.87 pg/ml, and the range was from 350 to 950 pg/ml in cases, and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml, serum copeptin was significantly higher in cases than controls.

Table (3): Comparison between study group outcome and control group outcome regarding Serum Copeptin:

	Cases group (n=58)		Control group (n=30)	**F**	**P-value**
	Term birth (n=51)	**Preterm birth (n=7)**			
Serum Copeptin(pg/ml) (Min. – Max.) Mean ± SD.	350 - 950 642 ± 163	400 - 900 751 ± 170	110 - 350 192.67 ± 71.16	104	0.001**
Post hoc test	P1=0.028* P2<0.001** P3<0.001**				

P1: Term birth vs Preterm, P2: Term birth vs Control, P3: Preterm birth vs Control
F: ANOVA test, p: p value for comparing between the studied groups **: Highly significant

Serum Copeptin mean was 642±163 pg/ml, and the range was from 350 to 950 pg/ml in cases with term birth, was 750±170 pg/ml, and the range was from 400 to 900 pg/ml in cases with preterm birth and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml, serum copeptin was significantly higher in cases with preterm birth than term birth and controls.

Table (4): Correlation between serum copeptin and the other parameters

	Serum Copeptin	
	r	**P**
Demographic data		
Age	-0.384	0.000**
BMI	-0.363	0.001*
Obstetric data		
Gravidity	-0.373	0.000**
Parity	-0.397	0.000**
GA	0.058	0.592
Cervical Length	-0.586	0.000**
Cervical dilatation	0.784	0.000**
Vital signs data		
MBP	0.084	0.435
Pulse	-0.148	0.168
RR	0.251	0.018*
Temp.	-0.117	0.278
Laboratory data		
HB	-0.071	0.508
WBCs	-0.333	0.002*
PLT	-0.301	0.004*
Urea	0.610	0.000**
Creatinine	0.705	0.000**
ALT	0.711	0.000**
AST	0.806	0.000**
INR	0.501	0.000**
RBG	0.394	0.002*

r: Spearman's correlation coefficient p: p value for comparing between the studied groups
**: Highly significant, *: significant

Serum copeptin was positively correlated with Cervical dilatation respiratory rate, Urea, Creatinine, ALT, AST, INR, and RBG. Serum copeptin was negatively correlated with age, BMI, gravidity, parity, cervical Length, WBCs, and PLT. Serum copeptin was not correlated with GA, MBP, pulse, temperature, and hemoglobin.

Table (5): Receiver operating characteristic (ROC) Curve and diagnostic indices of Copeptin for prediction of TPL

	AUC	P-value	95% Confidence Interval		Cut off Value	Sensitivity	Specificity	PPV	NPV
			Lower Bound	Upper Bound					
Copeptin	1.000	0.000**	0.999	1.000	≥ 380	98.3%	100%	100%	96.8%

AUC: Area Under a Curve p-value: Probability value
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$ **: Statistically highly significant at $p \leq 0.001$

ROC curve was used to determine the best cut off value of serum copeptin in predicting the threatened preterm labor. Our ROC results revealed that the serum copeptin cutoff value is ≥ 380 pg/ml and the area under the curve is equal to 1.00 which indicates that it is an excellent predictor. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

Discussion

Globally, preterm birth is the leading cause of perinatal mortality and morbidity. There is some chance of treating and preventing premature birth. To prevent needless expenses and adverse effects, a precise diagnosis and efficient treatment are crucial. Ensuring effective therapy may also help to lower perinatal morbidity or mortality (1).

Copeptin is a dependable measure of arginine vasopressin (AVP) and an endogenous stress marker.

During pregnancy, copeptin levels rise; in preeclamptic pregnancies, this rise is more pronounced than in normal pregnancies. Copeptin levels during the first trimester may also be a predictor of gestational diabetes and preeclampsia in the future (5; 6).

The aim of this study was to evaluate the role of maternal serum copeptin levels in diagnosis of threatened preterm labor and prediction of preterm birth.

This was a prospective case control study that was conducted on 88 pregnant women at Obstetrics and Gynecology Department, Faculty of Medicine, Menoufia University. All pregnant women included in this study were divided into two groups: Group I (Case group n=58): including pregnant ladies who were admitted for threatened preterm labor. We depended on painful uterine contractions and the existence of changes in the cervix for the diagnosis of preterm labor. Group II (Control group n=30): including 30 healthy pregnant ladies matching cases in age, parity and gestational age.

In our study, the cervical length mean in cases group was 32.08±9.04 mm and ranged from 25 to 50 mm, and in controls it was 42.77±5.88 mm ranging from 30 to 52 mm which was significantly higher in controls than in cases. On the other hand, cervical dilatation mean in cases was 2.26±1.26 cm, and the range was from 1 to 6 cm, and in controls it was zero, cervical dilatation was significantly higher in cases than controls.

In accordance, Tulmac et al. (1) reported that cervical dilatation and length showed a significant difference between the groups, suggesting that an appropriate risk assessment was done while constructing the groups.

It was observed that women who had cervical dilatation had a higher risk of preterm delivery, and that preterm birth was independently correlated with short cervical length (7).

According to Ibrahim and Ahmed (8), full-term delivery is usually related to a cervical length of greater than 2.3 centimeters. Furthermore, Fuchs et al. (9) shown that in a group presenting with painful contractions (< 32 weeks), a cervical length of < 15 mm was associated with a 5.5-fold greater risk (44%) of delivery within a week, whereas a cervical length of ≥ 15 mm was associated with a 2% risk. Transvaginal cervical length (CL) measurement is a good indicator of increased risk of spontaneous preterm birth, according to Hamzaoğlu et al. (10).

In our study, serum copeptin was significantly higher in cases than controls. serum Copeptin mean was 641.29±167.87pg/ml, and the range was from 350 to 950 pg/ml in cases, and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml.

This is in harmony with Tulmac et al. (1) who reported that, The threatened preterm labor group had a higher level of serum Copeptin 7.76(0.39–35.62) ng/mL compared to 6.23(1.64–36.88) ng/mL for control group.

Our findings were consistent with Foda and Abdel (11) who showed that level of copeptin was greater in patients in labor compared to those who are not in labor.

The level of copeptin in serum during pregnancy has been a subject of extensive research especially in the aspect of its relation to the complications of pregnancy (5). When it was initially examined in preeclamptic patients, it was discovered to be higher than in normotensive pregnant controls (12).

In our study, serum Copeptin mean was 642±163pg/dl, and the range was from 350 to 950 pg/dl in cases with term birth, was 750±170pg/dl, and the range was from 400 to 900 pg/dl in cases with preterm birth and in controls it was 192.67±71.16 pg/dl ranging from 110 to 350 pg/dl, serum copeptin was significantly higher in cases with preterm birth than term birth and controls.

A study by Yeung et al. (13) concluded that higher copeptin levels were associated with increased risk of preterm birth not affected by preeclampsia; however, the association did not persist after adjustment for race. Another study by Tulmac et al. (1) assessed the serum copeptin levels by categorizing the patients according to the state of their preterm and term deliveries. There was no difference between the groups. This may be due to larger sample size in that study.

In our study, serum copeptin was negatively correlated with age. This comes in agreement with Yeung et al. (13) who found that higher copeptin levels were significantly ($P<0.05$) related to younger maternal age. In contrary, Tuten et al (14) found that there was no correlation between copeptin level and maternal age.

In our study, serum copeptin was negatively correlated with BMI, while it was positively correlated with respiratory rate, Urea, Creatinine, ALT, AST, INR, and RBG. However, serum copeptin was not correlated with MBP, pulse and temperature.

Ghorab et al. (15) observed that serum copeptin levels have a positive correlation with the body mass index (BMI), blood pressure, serum creatinine, uric acid, ALT and AST.

Tuten et al (14) found that in women with preeclampsia, copeptin correlated positively with systolic and diastolic blood pressure, creatinine, AST, ALT. Also, Kehinde et al (16) showed that serum Copeptin level was positively correlated to serum transaminases.

ROC curve was used to determine the best cut off value of serum copeptin in predicting the threatened preterm labor. Our ROC results revealed that the serum copeptin cut-off value is $\geq$ 380 pg/ml and the area under the curve is equal to 1.00 which indicate that it is an excellent predictor. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

No previous studies have been done to determine the cutoff point of serum copeptin level in diagnosis of preterm labor or prediction of preterm birth. However, copeptin levels in the diagnosis and prognosis of preeclampsia have been the subject of numerous other research, all of which found copeptin to be potentially helpful. (13; 17;18).

In a study by Niranjani (19), ROC analysis is used to evaluate the third trimester marker's sensitivity and specificity as well as the diagnostic performance of the serum Copeptin. Serum Copeptin levels between the Pre-eclampsia group and the control group may be distinguished using the optimal cutoff value of 313.57 pg/ml, which results in 82.35% specificity and 96.30% sensitivity. 93.33% is the negative predictive value and 89.66% is the positive predictive value.

Another study by Ola Sayed Mohamed et al., (20) found that the cut off value of serum Copeptin in discriminating preeclampsia and control group was 280 pg/ml, with 80% specificity and 73.33% sensitivity.

Despite these promising findings we have found of serum copeptin, it is essential to acknowledge some limitations, including the relatively small sample size and single-center design of the study. Further large-scale, multicenter research is needed to validate the utility of serum copeptin in a broader population and to assess its potential clinical implications in the management of preterm labor.

Conclusion

Maternal serum copeptin levels can serve as a valuable diagnostic and predictive marker in cases of threatened preterm labor and preterm birth. More reliable results can be obtained with a larger number of patients.

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