

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20192461>

Original Research Article

Serum urocortin in preterm labor is it an effective biomarker?

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Received: 07 April 2019

Accepted: 06 May 2019

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ABSTRACT

Background: Preterm labor classically defined as delivery before completed 37 gestational weeks. Urocortin a biomarker that have raised recent research interest is a 40-amino acid neuropeptide related to the corticotrophin-releasing factor molecular family. Interestingly urocortin is produced by gestational tissue such as amnion and chorion predictability of preterm labor by biomarker assay could enhance management levels particularly in cases of preterm labor that are considered a frequent clinical scenario in obstetric practice. Aim of the study was to assess and evaluate the serum levels of urocortin predictability capacity in cases that develop preterm labor.

Methods: The current research clinical trial was conducted in a prospective way there was two research groups 60 study subjects had threatened preterm labor and 60 normal research study subjects that delivered at term. Comparative analysis was performed for urocortin assay conducted in both research groups in correlation to gathered clinical data obtained from both research groups.

Results: Receiver operating characteristic curve (ROC) between preterm and term delivery research groups as regards plasma urocortin level (pg/ml) as a predictor of pre term delivery showing that a cut-off point level >101.3 pg/ml in which statistical sensitivity=88.33%, statistical specificity=75%, positive predictive value=77.9, negative predictive value=86.5.

Conclusions: This research finding reveal that maternal serum urocortin is an effective biomarker in predictability of preterm labor; however future research studies should be multicentric in fashion putting in consideration the racial and ethnic differences besides the impact of BMI on maternal serum urocortin indices.

Keywords: Biomarker, Myometrial contractility, Preterm labor, Urocortin, Uteroplacental perfusion

INTRODUCTION

Preterm labor classically defined as delivery before completed 37 gestational weeks, preterm labor and prematurity issues are a frequent clinical scenario faced in every day obstetric practice that obligates the researchers all over the globe to investigate predictability tools on various basis such as sonographic, clinical, and biochemical markers.^{1,2}

Biomarkers are extensively investigated over the past two decades with variations in sensitivity and specificity levels, however the perfect universal biomarker is still not apparent for routine clinical practice.^{3,4}

Urocortin a biomarker that have raised recent research interest is a 40 amino acid neuropeptide related to the corticotrophin-releasing factor molecular family.⁵ Interestingly urocortin is produced by gestational tissue such as amnion and chorion; furthermore it could be assayed from maternal and fetal circulatory systems that could be implemented in clinical correlation to preterm labor impending clinical presentation.⁶

Urocortin have stable levels all over the three gestational trimesters and vary according to uterine activity quiescence and contractility and was observed to be increasing in preterm delivery cases particularly originating in large amounts from myometrial cells.⁷ At

molecular and cellular levels urocortin triggers the myometrial responsiveness to prostaglandins aiding in propagation and augmentation of the physiological process of delivery.⁸

On the other hand, in post term pregnancies it was observed, revealed, and displayed that serum levels of urocortin are reduced.⁹ All previous research findings denote that it could be possibly be implemented as a promising biomarker in early detection and predictability of preterm labor.¹⁰

The aim was to assess and evaluate the serum levels of urocortin predictable capacity in cases that develop preterm labor.

METHODS

This study was carried out in Saudi Arabia, in Jeddah at a private hospital (Bugshan Hospital) for a period starting from January 2011 to December 2018.

This research clinical trial is a prospective study in which there were two research groups 60 study subjects who had threatened preterm labor and 60 normal research study subjects that delivered at term all research study subjects were subjected to full clinical history, examination and other routine investigations besides the urocortin assay. Inclusive research criteria involved the following singleton gestations, presenting with threatened preterm labor from 28 till 36 gestational weeks. Exclusive research criteria involved the following cases with multi fetal gestations, fetal distress, DM, placental abruption, preeclampsia, IUGR, Fetal congenital anomalies, above 5 cm cervical dilatation, and infectious clinical signs.

Urocortin assay

Performed by radioimmunoassay having a sensitivity of around 50 pg/ml with intraassay and interassay variations of 6 and 8%, consecutively.

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. Quantitative data were presented as mean, standard deviations and ranges when parametric and median with inter-quartile range when non parametric, also qualitative variables were presented as number and percentages. The comparison between two groups regarding qualitative data was done by using Chi-square test, also groups with quantitative data and parametric distribution was done by using Independent t-test while with non-parametric data were compared using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation of plasma Urocortin level with gestational age (weeks) and with interval between

admission and delivery. Receiver operating characteristic curve (ROC) was used to assess the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) of plasma Urocortin level as a predictor for preterm labor and interval between admission and delivery. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value < 0.05 was considered significant.

RESULTS

Table 1 reveals and displays the comparative analysis of research data of the studied research groups in which age, parity, rupture of membranes, chorioamnionitis, gestational age at sampling there was no statistical significant difference between both research groups term and preterm delivery (p=0.163, 0.927, 0.832, 0.250, 0.257 consecutively). On the other hand, gestational age at time of delivery, birth weight, plasma urocortin levels were statistically highly significantly different between both research groups (p <0.001).

Figure 1 reveal and display that serum levels of plasma Urocortin were statistically significantly higher in preterm research group (p<0.001) term delivery research group versus preterm delivery research group Median (IQR)=93.95 (71.10-102.15) pg/ml versus 124.1 (110.99-146.76) pg/ml.

Table 2 reveals receiver operating characteristic curve (ROC) between preterm and term delivery research groups as regards plasma urocortin level (pg/ml) as a predictor of pre term delivery showing that a cutoff point level >101.3 pg/ml in which statistical sensitivity =88.33%, statistical specificity =75%, positive predictive value =77.9, negative predictive value=86.5.

Table 3 reveals and displays that there was no statistical significant difference between research study subjects delivered within one week of admission (n=47) and research study subjects who delivered more than one week after admission (n=13) as regards age, parity, rupture of membranes, chorioamnionitis, gestational age at sampling, gestational age at time of delivery (p values= 0.103, 0.217, 0.890, 0.899, 0.069 and 0.082 consecutively) whereas there was highly statistical significant difference between both compared research categorical groups as regards interval between admission, birth weight, plasma urocortin (pg/ml) (p<0.001, 0.001, <0.001 consecutively).

Table 4 reveal and display Receiver operating characteristic curve (ROC) between preterm delivered within 7 days of admission and those who delivered more than 7 days of admission in which cut off point level of serum urocortin >104.8 pg/ml IN which area under the curve=0.984, statistical sensitivity=97.87%, statistical specificity=92.31%, positive predictive value=97.9, negative predictive value=92.3.

Table 1: Comparison between term delivery and preterm delivery regarding the studied parameters (n=60).

	Term delivery	Preterm delivery	Test value	P value	Sig.
Age					
Mean±SD	27.95±2.87	28.73±3.21	1.403•	0.163	NS
Range	23–34	21–36			
Parity					
Median (IQR)	1 (1–2)	2 (0–2)	0.051‡	0.927	NS
Range	0–3	0–3			
Rupture of membrane					
Negative	46 (76.7%)	45 (75.0%)	0.045*	0.832	NS
Positive	14 (23.3%)	15 (25.0%)			
Chorioamnionitis					
Negative	42 (70.0%)	36 (60.0%)	1.319*	0.250	NS
Positive	18 (30.0%)	24 (40.0%)			
GA at sampling					
Mean±SD	31.2±1.2	30.9±1.65	1.139•	0.257	NS
Range	30 - 33	29–34			
GA at delivery					
Mean±SD	38.9±0.45	32.7±1.3	34.910•	<0.001	HS
Range	37.3–40.5	30.6–34.5			
Birth weight					
Mean±SD	3367.4±125.2	1967.3±147.15	56.133•	<0.001	HS
Range	2815–3750	1690–2540			
Plasma Urocortin (pg/ml)					
Median (IQR)	93.95 (71.10–102.15)	124.1 (110.99–146.76)	7.023‡	<0.001	HS
Range	50.4–160.7	90.18–172.3			

GA: Gestational age; NS: Non significant; HS: Highly significant; •: Independent t-test; ‡: Mann-Whitney test; *: Chi-square test.

Table 2: Receiver operating characteristic curve (ROC) between preterm and term delivery research groups as regards plasma Urocortin level.

Cut off point	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	+PV (95% CI)	-PV (95% CI)
>101.3	0.878 (0.806 to 0.931)	88.33 (77.4 - 95.2)	75.00 (62.1 - 85.3)	77.9 (66.2 - 87.1)	86.5 (74.2 - 94.4)

Table 3: Comparison between research study subjects who delivered within one week of admission and those who delivered more than one week of admission as regards the studied research parameters.

	Delivered within one week of admission n=47	Delivered more than one week of admission n=13	Test value	P value	Sig.
Age					
Mean±SD	27.98±2.58	29.48±3.84	1.658•	0.103	NS
Parity					
Median (IQR)	1 (0–2)	2 (1–3)	1.322‡	0.217	NS
Rupture of membrane					
Negative	37 (78.7%)	10 (76.9%)	0.019*	0.890	NS
Positive	10 (21.3%)	3 (23.1%)			
Chorioamnionitis					
Negative	28 (59.57%)	8 (61.54%)	0.016*	0.899	NS
Positive	19 (40.43%)	5 (38.46%)			
GA at sampling					
Mean±SD	31.45±2.02	30.35±1.28	1.856•	0.069	NS
Interval between admission	4.74±1.64	13.15±1.57	16.542•	<0.001	HS

	Delivered within one week of admission n=47	Delivered more than one week of admission n=13	Test value	P value	Sig.
and delivery					
GA at delivery			1.770•	0.082	NS
Mean±SD	32.38±1.01	33.02±1.59			
Birth weight			3.355•	0.001	HS
Mean±SD	1894.3±132.15	2040.3±162.15			
Plasma Urocortin (pg/mL)			5.482‡	<0.001	HS
Median (IQR)	135.7 (121.6–150.6)	99.4 (96.4–103.8)			
Range	102.27–172.3	90.18–115.8			

GA: Gestational age; NS: Non significant; HS: Highly significant. •: Independent t-test; ‡: Mann-Whitney test; *: Chi-square test.

Table 4: Receiver operating characteristic curve (ROC) between preterm delivered within 7 days of admission and those who delivered more than 7 days of admission.

Cut off point	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	+PV (95% CI)	-PV (95% CI)
>104.8	0.984 (0.911 to 1.000)	97.87 (88.7 - 99.9)	92.31 (64.0 - 99.8)	97.9 (88.5 - 99.9)	92.3 (64.0 - 99.8)

Table 5: Spearman correlation coefficients for the Plasma Urocortin level.

	Plasma Urocortin (pg/mL)	
	r	P value
Interval between admission and delivery	-0.596	<0.001 (HS)
GA (weeks)	-0.601	<0.001 (HS)

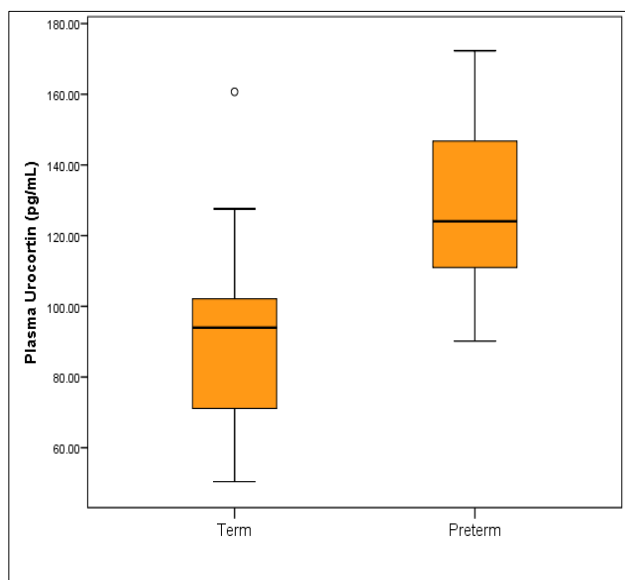


Figure 1: Plasma urocortin level (pg/ml) in term and preterm delivery research groups.

Table 5 reveal and display that by Spearman correlation coefficient statistical analysis that plasma urocortin level is highly statistically significant as regards interval between admission and delivery and gestational age (weeks) $p < 0.001$.

DISCUSSION

The research evidence obtained by histopathological research studies revealed that urocortin present in maternal circulation is chiefly from fetal tissues interestingly increasing the research debate and interest about the cross talk between the fetal and maternal systems in maintaining uterine quiescence besides trigger and upkeep of preterm labor.¹¹

Prior Research findings reveal and display that preterm labor could be correlated with reduction in vascular resistance of fetal cerebral circulatory blood flow; besides fetal urocortin secretory pattern is linked with uteroplacental blood perfusion pattern.¹² In addition, urocortin has shown to have considerable and persistent hemodynamic impact against hypoxia in experimental research animals.³ Therefore, it is reasonable to consider that urocortin secretion could safeguard the fetus from the hypoxic insult sequelae.⁵

This research study findings revealed and displayed that by comparative statistical analysis of research data of the studied research groups in which age, parity, rupture of membranes, chorioamnionitis, gestational age at sampling there was no statistical significant difference between both research groups term and preterm delivery ($p = 0.163, 0.927, 0.832, 0.250, 0.257$ consecutively). On the other hand, gestational age at time of delivery, birth

weight, plasma Urocortin levels were statistically highly significantly different between both research groups ($p < 0.001$). Furthermore receiver operating characteristic curve (ROC) between preterm and term delivery research groups as regards plasma Urocortin level (pg/ml) as a predictor of pre term delivery showing that a cutoff point level >101.3 pg/ml in which statistical sensitivity =88.33%, statistical specificity =75%, positive predictive value =77.9, negative predictive value=86.5.

Additionally our research study findings revealed and displayed that there was no statistical significant difference between research study subjects delivered within one week of admission ($n=47$) and those who delivered more than one week after admission ($n=13$) as regards age, parity, rupture of membranes, chorioamnionitis, gestational age at sampling, gestational age at time of delivery (p values=0.103, 0.217, 0.890, 0.899, 0.069 and 0.082 consecutively. Whereas there was highly statistically significant difference between both compared research categorical groups as regards interval between admission, birth weight, plasma urocortin (pg/ml) ($p < 0.001$, 0.001, < 0.001 consecutively).

Finally Receiver operating characteristic curve (ROC) between preterm delivered within 7 days of admission and those who delivered more than 7 days of admission in which cut off point level of serum urocortin >104.8 pg/ml IN which area under the curve =0.984, statistical sensitivity =97.87%, statistical specificity =92.31%, positive predictive value=97.9, negative predictive value=92.3, Spearman correlation coefficient statistical analysis have shown that plasma urocortin level is highly statistically significant as regards interval between admission and delivery and gestational age (weeks) $p < 0.001$.

A prior research study similar to the current research in methodology and approach have revealed and displayed that cases having threatened preterm labor have raised plasma levels of urocortin another research team of investigators have assayed the serum urocortin levels displaying its significantly raised levels in preterm labor cases and cases with impending delivery issues.^{1,4} Those research findings could be justified by the fact urocortin peptide triggers at cellular and molecular levels the myometrial contractility as displayed by in vitro research studies furthermore research groups of investigators priory compared and contrasted between serum urocortin in full term and preterm deliveries revealing and displaying the considerable rise of its levels even at the time of full term delivery.¹³

A prior cohort research study performed on pregnant cases at 28–36 gestational weeks having spontaneous preterm labor. Serum urocortin was assayed from all research study subjects. The cases recruited for the study were followed up till time of delivery and serum level of urocortin were statistically compared between cases having preterm delivery and those who delivered at term

(37 gestational weeks). The research team revealed and displayed the following research results in which from the One hundred and sixty research study subjects: One hundred and forty-eight (92.5%) of the cases had preterm delivery. Mean serum level of urocortin within the preterm delivery research group have been greater than in the Term research group, but not in a statistically significant fashion (392.6 ± 29.23 versus 113.2 ± 11.0 pg/mL, consecutively, $p = 0.252$). Area under the ROC curve =0.6, revealing that serum urocortin assay is not suitable appropriate for predictability preterm labor those research findings contradict with our research study findings.^{2,7,11}

CONCLUSION

The current research findings reveal that maternal serum urocortin is an effective biomarker in predictability of preterm labor, however future research studies should be multicentric in fashion putting in consideration the racial and ethnic differences besides the impact of BMI on maternal serum urocortin indices.

Furthermore, future research studies should be implemented with larger sample sizes that could aid in future clinical guideline implementation that would enhance management protocols in those cases.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rund NMA. Serum urocortin in preterm labor is it an effective biomarker? *Int J Reprod Contracept Obstet Gynecol* 2019;8:2522-7.