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Value of serum urocortin concentration in the prediction of preterm birth

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Abstract

Aim: Preterm delivery is a serious problem during pregnancy with remarkable neonatal adverse effects. Prediction of preterm delivery in women with preterm uterine contractions or signs of preterm labor is critical because if these women are identified they can be referred to tertiary centers. The present study aimed to evaluate the value of maternal serum urocortin concentration for predicting preterm delivery in women with signs of spontaneous preterm labor.

Material and Methods: A cohort study was conducted on pregnant women at a gestational age of 28–36 weeks who were admitted to the labor ward with spontaneous preterm labor. A blood sample was obtained from all participants to measure serum urocortin. The women were monitored up to delivery and serum urocortin was compared between women with preterm delivery and those who delivered at term (37 weeks of gestation). Receiver Operating Characteristic (ROC) curve analysis was used to determine sensitivity and specificity if applicable.

Results: One hundred and sixty pregnant women finished the study. One hundred and forty-eight (92.5%) of the women delivered preterm. Mean serum urocortin in the preterm delivery group was higher than in the term group, but without statistical significant difference (392.6 ± 29.23 vs 113.2 ± 11.0. pg/mL, respectively, $P = 0.252$). Area under the ROC curve was 0.6, which shows that this test is not appropriate for predicting preterm delivery in women with preterm labor.

Conclusion: Serum urocortin could not predict women who delivered preterm among women with signs of preterm labor.

Key words: plasma urocortin, pregnancy, preterm birth, preterm delivery, preterm labor.

Introduction

Spontaneous preterm labor is one of the most serious problems during pregnancy and is the main cause of neonatal morbidity and mortality, even in developed countries[1,2]. It is responsible for around one-third to 40–45% of preterm births[3,4] and is defined as the beginning of spontaneous uterine contractions before 37 completed weeks of pregnancy and is the main reason for two-thirds of deaths in the first year of life.[4–6] In addition, there is an increase neonatal morbidity caused mainly by prematurity of different body organs in births before 37 weeks compared to term deliveries.[5]

With regard to the above-mentioned problems, *in uteri* transfer of fetus in women with signs and symptoms of preterm labor to tertiary centers and centers with well-equipped neonatal intensive care unit (NICU) is under serious consideration.

The identification of women with threatened preterm labor who finally deliver preterm is especially important, because the capacity of NICU and tertiary centers is limited, especially in developing countries.

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Different biochemical markers including urocortin have been studied to find the best one to differentiate between preterm labors that end in preterm delivery, and those that do not.[7] Only with accurate and early identification of pregnant women who will have preterm delivery can interventions be established to postpone preterm delivery.[7]

The present use of these biomarkers in clinical practice is limited. By increasing the knowledge of the etiology and pathophysiology of preterm labor, these markers might be used more effectively to predict preterm delivery in preterm labor.

The purpose of the present study is to evaluate the diagnostic value of plasma urocortin concentration for predicting preterm delivery in women with signs of spontaneous preterm labor.

Material and Methods

A cohort study was performed on women who had been admitted to the labor ward of Akbarabadi Teaching Hospital in Tehran, Iran between March 2009 and March 2010 with signs of spontaneous preterm labor.

A sample size of 145 women was considered sufficient ($\alpha = 5\%$, sensitivity 80% and specificity 94%). Written informed consent was obtained from all participants, and institutional review board approval and institutional ethics committee approval was given to the study.

Inclusion criteria were gestational age between 28 and 36 weeks of pregnancy (according to a reliable last menstural period date and ultrasound confirmation of the first trimester), nuligravid, singleton, cephalic presentation, intact membranes, uterine contractions with a frequency of four contractions during 20 min and cervical dilatation and effacement of at least 1 cm and 50%, respectively. Exclusion criteria included cervical dilatation of 3 cm or more, vaginal bleeding, ruptured membranes, signs of chorioamnionitis, fetal distress, polyhydramnios, fetal anomalies, fetal death, intrauterine growth restriction (IUGR), any maternal factors in which continuation of pregnancy is unsafe for mother, like preeclampsia and other medical disorders, and smoking and drug abuse.

One milliliter of blood was obtained from all eligible participants before any drug prescription (betamethasone and tocolytics). Serum samples were preserved in –20°C up to the time of urocortin measurement using ELISA method (UNC1, Transhold Navigation Technology Co. Ltd, China). All women were monitored to delivery (either term or 37 completed weeks of pregnancy or preterm). The urocortin of these two groups (both term and preterm deliveries) was compared.

Statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). χ^2, Fisher's exact, Spearman's correlation coefficient, and Mann–Whitney tests were used to compare the data.

Receiver Operating Characteristic (ROC) curve analysis was used to determine the sensitivity and specificity. $P < 0.05$ was considered significant. In ROC curve, maximum diagnostic accuracy (100% sensitivity and 100% specificity) may be obtained when the area under the curve is 1, and the minimum diagnostic accuracy is when the area under the curve is 0.5.

Results

One hundred and sixty women completed the study. One hundred and forty-eight subjects of 160 (92.5%) delivered preterm and only 12 women (7.5%) delivered beyond 37 weeks of gestation (term). Twenty-seven women (16.8%) delivered at less than 32 weeks and 121 women (75.6%) delivered between 32 and 36 weeks. The characteristics of the women are shown in Table 1.

The mean interval between onset of labor up to delivery was 5.78 ± 6.59 days (range 0–42 days). Fifty-four women (33.8%) delivered in less than 48 h.

Mean plasma urocortin was 381.5 ± 27.98 pg/mL. Mean plasma urocortin was 392.6 ± 29.23 in preterm deliveries versus 113.2 ± 11.04 pg/mL in term deliveries, which showed a higher amount, but was not statistically significant ($P = 0.252$).

Table 1 Characteristics of the samples

Characteristic	Mean ± SD	Minimum	Maximum
Maternal age (years)	25.6 ± 4.7	17	38
Body mass index	26.4 ± 4.1	18.6	41.2
Neonatal weight (g)	2303.5 ± 650.2	1150	4150
Gestational age (weeks)	33.6 ± 2.4	28	36
Interval between sampling and delivery (days)	5.78 ± 6.59	0	42

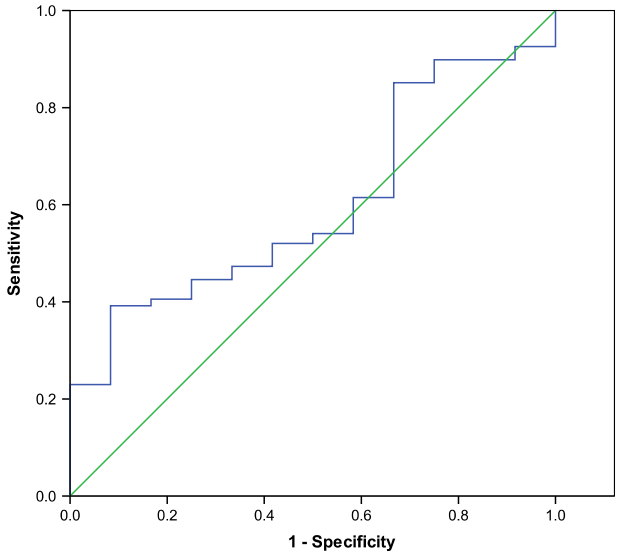

Figure 1 Receiver operating characteristic curve of serum urocortin level for prediction of preterm delivery. The area under the curve is 0.6, which shows no significant predictive value of plasma urocortin.

There was no statistically significant correlation between plasma urocortin and maternal age ($P = 0.692$, Pearson's correlation coefficient = –0.032), neonatal weight ($P = 0.544$, Spearman's correlation coefficient = 0.048), body mass index ($P = 0.555$, Pearson's correlation coefficient = –0.047), and gestational age ($P = 0.732$, Spearman's correlation coefficient = 0.027).

A weak correlation was found between plasma urocortin level and the interval between the start of labor pain up to delivery (i.e. as this interval increased, the plasma urocortin decreased) ($P = 0.042$, Spearman's correlation coefficient = –0161).

Even though the mean concentration of plasma urocortin showed a remarkable difference between the two groups of term and preterm deliveries, the Mann–Whitney test could not show any statistically significant difference. ROC curve was used to show the diagnostic accuracy of urocortin for predicting preterm deliveries.

The area under the curve was 0.6, which showed no significant predictive value of plasma urocortin (Fig. 1).

In addition, ROC curve was used to show the diagnostic accuracy of plasma urocortin for predicting of delivery in less than 48 h in the cases of preterm labors. The area under the curve was 0.618, which showed no diagnostic value for prediction of delivery in less than 48 h from the beginning of labor pain.

The area under curve was 0.5 in the ROC curve for showing the diagnostic value of plasma urocortin for prediction of deliveries of less than 32 weeks, which also showed no significant diagnostic value for this purpose.

Discussion

Despite a higher concentration of plasma urocortin in preterm deliveries compared with term deliveries, the difference was not statistically significant. This result might be because of the small number of term deliveries (7.5%) and because the Mann–Whitney test could not show any statistically significant difference.

In the present study 92.5% of women delivered preterm, 16.8% delivered in less than 32 weeks and 75.6% delivered between 32 and 36 weeks. These results indicate that after establishment of the labor, it is too late to measure plasma urocortin to predict preterm deliveries among women with preterm labor and measurement should be performed sooner, even as early as the first painful uterine contractions. Therefore, plasma urocortin measurement is not helpful in cases of established preterm labors. If this measurement was made earlier in the course of preterm labor, it might be helpful.

Some of the tests that have been evaluated for prediction of preterm delivery in cases of preterm labor include measurement of crevice vaginal prolactin and fetal fibronectin, C-reactive protein (CRP) measurement in amniotic fluid and plasma, measurement of amniotic fluid interleukin-6, TNF-alpha, cytochrome C, and cell death nucleosomes, human chorionic gonadotropin hormone (HCG) measurement in cervicovaginal secretion and measurement of interleukin-8 in cervicovaginal fluid.[8,9]

Recently, analysis of the transcriptome (transcriptomics) and protein composition (proteomics) of amniotic fluid has been used to assess the risk of preterm delivery in patients with spontaneous preterm labor.[10]

Other reported markers are stress hormones, including maternal plasma urocortin and corticotrophin-releasing hormone (or factor) (CRF, CRH).

Urocortin is a neuropeptid with 40 amino acids, which belongs to corticotropin releasing factor (CRF) with a high affinity to both receptor types I and II.[11] It is secreted from deciduas, chorion, amnion, trophoblasts, and myometrium and is measurable in maternal plasma from the first trimester to the third trimester.[11] Urocortin concentration also changes during quiescence or contractions of myometrium and increases

in preterm labor,[12] but shows a decrease in cases of post-term pregnancies in comparison with term pregnancies.[13]

At the same time, urocortin concentration may directly increase (potentiate) uterine contractions through increasing myometrial contractile response to prostaglandins.[14]

Florio *et al*.[11] showed an increase in urocortin concentration in women with signs of preterm labor who eventually delivered preterm. They concluded that its measurement in plasma might be used as a marker for prediction of preterm delivery (birth). Another study[15] by the same researchers stated that neither urocortin nor CRF concentrations change during the labor process or in different stages of labor after the onset of labor, while there were increases at the beginning of labor compared with the earlier months of pregnancy.

Makrigiannakis *et al*.[16] reported a higher concentration of plasma CRH and ACTH in women with preterm labor who eventually delivered preterm.

Other researches,[18] have measured CRH in the second trimester and found it to be higher in women who finally had preterm labor. Some researchers concluded that CRH measurement might be used in conjunction with other predictive tests of preterm delivery to make them more reliable and more accurate and complete.[17] In contrast, the other study,[19] which is in agreement with the present study, showed that despite higher concentration of plasma CRH in preterm deliveries, it had no significant predictive value and concluded that its measurement is not important in the clinical practice.

CRH level has shown a relationship with maternal stress,[18] and its role has been considered key in producing preterm labor in cases of prenatal stress.[20]

Torricelli *et al*.[21] stated that stress-related steroidal hormones are involved in the pathogenesis of preterm labor, even if their clinical usefulness as a marker for predicting preterm labor is not clear. CRF and urocortin both belong to these stress hormonal groups.

Amniotic fluid urocortin and CRF have been measured in the second trimester of pregnancy,[21] and the present study showed less amniotic fluid urocortin in cases of preterm delivery in comparison term deliveries, but CRF and other steroidal hormones did not show a significant difference. The result of this study might present the fact that in the second trimester of pregnancy their mechanism of action might not have been activated.

Unfortunately there are few studies on urocortin; therefore, its role in the prediction of preterm delivery in cases of preterm labor remains unclear. The abovementioned studies also did not show similar results; therefore, it is necessary to perform more studies to elucidate its effects and practical usage.

Disclosure

None declared.

References

1. Louden JA, Groom KM, Bennett RR. Prostaglandin inhibitors in preterm labor. *Best Pract Res Clin Obstet Gynaecol* 2003; **17**: 731–744.
2. Kam KY, Lament RF. Developments in the pharmacotherapeutic management of spontaneous preterm labor. *Expert Opin Pharmacother* 2008; **9**: 1153–1168.
3. Tan TC, Devendra K, Tan LK, Tan HK. Tocolytic treatment for the management of preterm labour: A systematic review. *Singapore Med J* 2006; **47**: 361–366.
4. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse D, Spong CY. *Williams Obsterics*, 23rd edn. New York: McGraw-Hill, 2010; 804–832.
5. Mathews TJ, Mac Dorman MF. *Infant Mortality Statistics from the 2005 Period Linked Birth/Infant Death Data Set. National Vital Statistics Reports*. Vol 57, No 2 Hyattsville, MD: National Center for Health Statistics, 2008.
6. Eichenwald EC, Stark AR. Management and outcome of very low birth weight. *N Engle J Med*. 2008; **358**: 1700–1705.
7. McGrath S, Smith R. Prediction of preterm delivery using plasma corticotropin-releasing hormone and other biochemical variables. *Ann Med* 2002; **34**: 28–36.
8. Honest H, Forbes CA, Duree KH *et al*. Screening to prevent spontaneous preterm birth: Systematic reviews of accuracy and effectiveness literature with economic modeling. *Health Technol Assess* 2009; **13**: 1–627.
9. Puchner K, Lavazzo C, Gourgiotis D *et al*. The implication of second-trimester amniotic fluid TNF-alpha, cytochrome C, and cell death nucleosomes in the prediction of preterm labor and/or premature rupture of membranes. *Arch Gynecol Obstet* 2011; **285**: 37–43. Apr 28 [Epub ahead of print].
10. Romero R, Mazaki-Tovi S, Vaisbuch E *et al*. Metabolomics in premature labor: A novel approach to identify patients at risk for preterm delivery. *J Matern Fetal Neonatal Med* 2010; **23**: 1344–1359.
11. Florio P, Linton EA, Torricelli M, Faldini E, Reis FM, Imperatore A. Prediction of preterm delivery based on maternal plasma urocortin. *J Clin Endocrinol Metab* 2007; **92**: 4734–4737.
12. Florio P, Torricelli M, Galleri L, De Falco G, Leucci E, Calonaci G. High fetal urocortin levels at term and preterm labor. *J Clin Endocrinol Metab* 2005; **90**: 5361–5365.
13. Torricelli M, Ignacchiti E, Giovannelli A, Merola A, Scarpetti E, Calonaci G. Maternal plasma corticotropin-releasing factor and urocortin levels in post-term pregnancies. *Eur J Endocrinol* 2006; **154**: 281–285.
14. Petraglia F, Florio P, Benedetto C, Marozio I, Di Blasio AM, Ticconi C. Urocortin stimulates placental adreno corticotropin

and prostaglandin release and myometrial contractility in vitro. *J Clin Endocrinol Metab* 1999; **84**: 1420–1423.
15. Florio P, Cobellis L, Woodman J, Severi FM, Linton EA, Petraglia F. Levels of maternal plasma corticotropin-releasing factor and urocortin during labor. *J Soc Gynecol Investig* 2002; **9**: 233–237.
16. Makrigiannakis A, Semmler M, Briess V, Eckerle H, Minas V, Mylonas I. Maternal serum corticotropin-releasing hormone and ACTH levels as predictive markers of premature labor. *Int J Gynacol Obstet* 2007; **97**: 115–119.
17. McLean M, Bisits A, Davies J *et al*. Predicting risk of preterm delivery by second-trimester measurement of maternal plasma coricotropin-releasing hormone and alfa-fetoprotein concentrations. *Am J Obstet Gynecol* 1999; **181**: 207–215.
18. Hobel CJ, Dunkel-Schetter C, Roesch SC, Castro LC, Arora CP. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. *Am J Obstet Gynecol* 1999; **180**: 257–263.
19. Coleman MA, France JT, Schellenberg JC, Ananiev V, Townend K, Keelan JA. Corticotropin-releasing hormone, corticotropin-releasing hormone-binding protein, and active A in maternal serum: Prediction of preterm delivery and response to glucocorticoids in women with symptoms of preterm labor. *Am J Obstet Gynecol* 2000; **183**: 643–648.
20. Wadhwa PD, Porto M, Garite TJ, Chicz-De Met A, Sandman CA. Maternal corticotropin- releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. *Am J Obstet Gynecol* 1998; **179**: 1079–1085.
21. Torricelli M, Voltolini C, Galleri L, Biliotti G, Giovannelli A, De Bonis M. Amniotic fluid urocortin, CRF, oestriol, dehydroepiandrosterone sulfate and cortisol concentrations at mid-trimester: Putative relationship with preterm delivery. *Eur J Obstet Gynecol Reprod Biol* 2009; **146**: 169–173.