

Vitronectin and prolactin levels of cervicovaginal irrigation liquid in preterm birth risk evaluation

Ebru Inci Coskun¹, Salim Sezer², Ismail Dag³, Ercan Yilmaz¹, Yavuz Tahsin Ayanoglu⁴

¹Inonu University, Faculty of Medicine, Department of Gynaecology and Obstetrics, Malatya, Turkey

²Istanbul Kanuni Sultan Suleyman Research And Training Hospital, Clinic of Gynaecology and Obstetrics Division of Perinatology, Istanbul, Turkey

³Istanbul Eyüp State Hospital, Clinic of Biochemistry, Istanbul, Turkey

⁴Istanbul Taksim Research and Training Hospital, Clinic of Gynaecology and Obstetrics, Istanbul, Turkey

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Abstract

Aim: The objective of this study is to determine the predictive role of cervical length, cervicovaginal irrigation liquid vitronectin and prolactin levels in preterm birth.

Material and Methods: A total of 73 pregnant women between 24-34th gestational week were included and the study population was divided into two groups as: term birth group (n=54) and preterm birth(n=19). Birth weeks, weight and methods were noted. The irrigation fluid has been collected from posterior fornix and vitronectin levels are detected by Enzyme-linked-immunosorbent-assay method.

Results: Vitronectin were higher in preterm group as compared to controls [90 (78-98) vs 16 (9-41) ng/ml, p<0.001]. Positive predictive value for vitronectin was 78 %, negative predictive value was 100 % and accuracy ratio was 91.8%. The sensitivity of vitronectin was 100 %, specificity was 89 % with a cut-off value of 59 ng/mL. Area under curve for vitronectin was 0.96 which was compatible with 'perfect'. When average prolactin levels have been found as 0.14 ng/mL in term and 2 ng/mL in preterm birth group, cervical length have been found as 34.5 and 24.2 mm respectively. Cut-off value for prolactin has been found as 0.088 ng/dL. Positive predictive value was 58.3 % for prolactin and 51.5 % for cervical length. Negative predictive value was 89.8% for prolactin and 95 % for cervical length. Vitronectin was strongly positively correlated with prolactin levels while it was negatively correlated with cervical length (r=0.691 and r=-0.348 respectively).

Conclusion: Many trials have been done to make the most accurate prediction of preterm delivery risk. By this study, it makes us think about that vitronectin could be a valuable marker for preterm birth, and also could be independent from the gestational week.

Keywords: Preterm birth; vitronectin; prolactin; cervical length; vaginal irrigation; risk evaluation

INTRODUCTION

Preterm delivery is the presence of powerful and periodic contractions those cause progressive dilatation and effacement of cervix between the 20th and 37th weeks of gestation. It complicates approximately 6-13 % of the pregnancies all over the world though it differs among countries (1,2). Preterm birth has been associated with 80 % of perinatal mortality so is the most common cause of fetal deaths those not associated with fetal anomalies. That's why preterm birth is a health issue that never loses its importance worldwide (3).

Another communal importance of preterm birth is the sources used for the nursing of these infants. While the effects of preterm birth on terms of newborn, adolescent and adulthood, especially adulthood diseases like hypertension and diabetes, this economic status has become more comprehensive (4-7). It should be considered that additional expenses could be required in childhood because of the developmental and behavioral disturbances caused by long term outcomes. As a consequence, it has been estimated that obstetrics decisions are so important by the lowest edge of gestational age while the survival rate improves every single day

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Corresponding Author: Ebru Inci Coskun, Inonu University, Faculty of Medicine, Department of Gynaecology and Obstetrics, Malatya, Turkey E-mail: ebruincicoskun@gmail.com

(8). While short term morbidities of preterm delivery are respiratory difficulties, intraventricular hemorrhage, periventricular leucomalacia, necrotising enterocolyte, bronchopulmonary dysplasia, sepsis and patent ductus arteriosus, the long term morbidities are cerebral palsy, mental retardation and premature retinopathy, the risk of which are correlated directly with gestational age and birth weight (8, 9).

There have been essentially four causes of preterm labor: 1) Induced preterm labor or cesarean section for maternal and fetal indications. 2) Spontaneous unexplained preterm labor with intact membranes 3) Idiopathic preterm premature membrane rupture 4) Preterm labor of multiple gestations (10).

The pathogenesis of preterm delivery has not been understood well. It has not been clear that if it has been triggered by idiopathic activation or by a pathologic mechanism. In normal delivery, cervical softening, cervical maturation before active labor phase and the molecular mechanisms of the myometrium in that phase can explain the process by activation of these mechanisms before the time it should be activated. Maybe the prevention of these mechanisms can block the preterm labor and these can give ideas about new trials of this issue. If the preterm birth can not be prevented, precautions and appropriate management should be done properly for diminishing morbidity and mortality.

Recently, there have been a lot of methods and biochemical markers used to predict preterm delivery. Some of these are transvaginal measurement of cervical length, granulocyte elastase in cervical secretions, fetal fibronectin, maternal serum C-reactive protein, alpha-fetoprotein, insulin-like growth factor binding protein-1, prolactin, beta-HCG, progesterone, and estrogen (11).

One of the first noticed hormones produced by decidua has been prolactin. It has been shown that prolactin has been produced by chorionic cytotrophoblast, decidua, amnion and placental syncytiotrophoblast (12,13). Therefore prolactin has been mentioned as a candidate of these studies for the prediction of preterm delivery besides some other pregnancy complications (14,15).

Cervical length measurement with vaginal probe has been a popular, considerably studied method and it needs attention. Iams and colleagues have measured cervical length of 2915 women at 24 th and 28 th weeks of pregnancy and they have found the average cervical length in 24th week as 35 mm and the shorter the length of cervix the more often occurred the preterm delivery (16).

Vitronectin, also known as VTN, is one of the cellular adhesion molecules with fibronectin (17). There have been many binding regions of VTN like the other adhesive glycoproteins: N-terminal Somatomedin B domain, Hemopexin like central domain and C-terminal domain (18). Somatomedin B domain of vitronectin has bound to plasminogen activator inhibitor-1 and stabilizes it. Thus, vitronectin regulates the proteolysis started with the activation of plasminogen and plays a role in regulation

of proteasins cascade that controls the matrix turnover (19). RGD (Arg-Gly-Asp) sequence follows the N-terminal Somatomedin B domain and this region is a common recognition region for many integrins. C terminal is rich in arginine and responsible for heparin binding activity. Besides, converges with C5b-7 complex of complement and thrombin-antithrombin complexes.

Vitronectin, has an important role in healing, too. Especially polymorphonuclear leucocytes migrate over the vitronectin. Adhesion of endothelial cells with vitronectin or fibronectin causes an increase of calcium in the cell. The migration of cells over VTN is also related to calcium, especially extracellular ionized calcium. Cell migration is regulated by cytokines in some kind of cells and by integrins in some kind of cells, so vitronectin has a pivotal role in angiogenesis, migration of endothelial cells.

Liver is the primary origin of the plasma vitronectin. Animal trials showed that VTN expression has been occurred in especially liver, blood vessels and neuroectodermal origin tissues. Embryonic lungs, muscles and renal basal membrane matrix have been shown that includes vitronectin. It has also been found related to complement activity in dermal elastic fibres of human skin, skin lesions of dermatomyositis and atherosclerotic plaques. Vitronectin has been also increased in the lesions of multiple sclerosis (20). Furthermore, VTN has found to be altered in malignancy. It has been detected in stroma of colorectal adenocarcinoma and advanced stage malignant astrocytoma. It has been considered that the microenvironment of tumour has been a regulatory for the VTN gene expression. It has been reported that high levels of both plasminogen activator inhibitor-1 and urokinase receptors are related to the poor prognosis of cancer patients. Cell adhesion and migration has a direct role in metastasis of cancer, so these common mechanisms can be explanatory. While the factors inducing vitronectin synthesis presented, the control of vitronectin levels in tumoral tissue could be a pivotal treatment area (20,21).

In gum connective tissue VTN exists spreadly with fibronectin. It has roles in cell adhesion, migration, wound healing, and oncogenic transformation as well. Moreover it has a storage duty for several cytokines and growth factors with fibronectin. Besides the mammalian cells, vitronectin, binds to many bacterial cell surface. *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* species, some of them recognized so far (22).

Briefly the several roles of vitronectin both in circulation and in extracellular matrix, are because of its interactions with many humoral and cellular proteins (23, 24).

Integrins, regulate many cell functions like cell migration, proliferation and cell behavior, in almost all kinds of cell (25). Integrins are a large family of cell surface receptors. The speed of the cell migration depends on the loss of integrins left behind by the cell and the broken contacts of adhesions (26). That deserves an attention for the role of vitronectin and integrins in tumor progression and

invasion. There have been a lot of reports about central nervous system tumors like glioma and a lot of other system tumors (27).

The objective of this study is to determine the predictive role of transvaginal cervical length, vitronectin and prolactin levels of the cervicovaginal irrigation liquid in preterm birth.

MATERIAL and METHODS

Pregnants in between 24th and 34th weeks of gestation who admitted to Taksim Research and Training Hospital Pregnancy Outpatient Clinics and Bakırkoy Women and Children Hospital for routine antenatal follow up between November 2008 and March 2009 were included. Ethical approval has been taken from the Ethics Committee of Bakırkoy Women and Children Hospital. The aim has been to make the correct prediction if the patient would have preterm birth or term birth. That's why it was not important whether the patient has any symptoms or not. The time of birth as preterm or term was the important point in the study. Therefore we did not separated the patients into groups as with symptoms or without symptoms. Before the examination, an information form has given to the patients and then oral and written approvals have been taken from the patients which would like to be placed in the study. Patients which have vaginal hemorrhage, membrane rupture or pregnant those have cervical dilatation > 3 cm, patients with placenta previa, hypertension or pre-eclampsia, patients with congenital fetal anomalies, fetal restriction of growth or multiple gestation and the patients who need induction because of maternal or fetal causes, are excluded from the study.

Objective of this study has been to make the right prediction if the patient would have preterm birth or not. That's why it was no matter if the pregnant was symptomatic or not. So we did not separated the groups according to the existence of symptoms.

After anamnesis and information leded approvals, patients are examined. After vulvar inspection, vaginal and cervical inspection has done by a disposable speculum, gently. An irrigation fluid composed of 0.9 % NaCl has been prepared as 3 cc under sterile conditions before the examination. Half of the irrigation fluid drained to the external cervical os and the other half drained to vaginal fornix by not touching to the tissues with the needle pin. The poured fluid in the spekulum poCKET in the posterior vagina has been aspirated by another injector and the speculum has been taken out. Cervix has been evaluated by transvaginal ultrasonography, the cervix magnified 3/4 of the monitor, the cervical internal os, external os and cervical canal have been visualized in the sameline then the cervical length measurement has been undertaken. The irrigation fluid collected from the posterior vagina has been centrifuged 2000 g force for 10 minutes by Hettich-Rotanta 460 r centrifuge. Supernatant fluid has been preserved at -40 °C.

Birth weeks, weights of newborns and the birth methods are noted, the pregnant who have birth other than our study hospitals are called by telephone and the informations are gained. 80 patients have been taken for the study, but 5 of them could not be reached after the study. One of the tubes that contain irrigation fluid collected from a patient was broken and one of the tubes has been poured in the centrifuge. So 7 patients have been ruled out of the study, statistical analysis has been done for 73 patients. Pregnants having birth after 37th week and later have been admitted as term, before 37th week, has been admitted as preterm. 19 of the 73 patients had preterm birth, 54 had birth in term weeks. These two groups are compared.

Cervicovaginal vitronectin levels are detected by Enzyme Linked Immunosorbent Assay (ELISA) method using 'Human Vitronectin Total Antigen Assay' (antibody covered 96-well plate human Vitronectin) commercial kit belongs to Innovative Research Laboratory (46430 Peary Court Novi, Michigan 48377). Adsorbance measurements has been done at Biomedical Technologies Inc. USA ELx800 (Bio-Tek Instruments Inc) microplate reading at 450 nm. Cervicovaginal prolactin levels are detected by Electro Chemiluminescence Immune Assay (ECLIA) method using Roche Diagnostic commercial kit at 'Roche/Hitachi Modular Analytics E170' autoanalyzer.

Statistical analysis

All statistical analysis has been performed with SPSS 11.5. Relevance of Gauss distribution of continous variables is tested and normal distributed continous variables (cervical length, birth week, birth weight) are shown as mean±SD; nonnormally distributed continous variables (prolactin, vitronectin and the week of examination) are shown as median (25. percentile-75. percentile).

For comparison of independent groups, Student t test and Mann-Whitney U test have been used. In comparison of predicted and observed values, Chi-Square test has been used. Correlation between variables has been evaluated by Spearman correlation coefficient (rs) and Pearson correlation coefficient (r). In determination of the sufficiency of the tests, Receiver Operator Characteristics (ROC) curves have been used. Statistically significance has been evaluated as p < 0.05 (two-tailed).

RESULTS

A total of 73 pregnant women were analysed and the study population was divided into two groups as: term birth group (n=54) and preterm birth (n=19). The data of variables for term and preterm birth groups were demonstrated in Table 1. There was statistically significant difference between term and preterm birth group according to birth time, birth weight, cervical length, and prolactin levels. Furthermore, vitronectin levels were significantly higher in preterm birth group as compared to controls [90 (78-98) vs 16 (9-41) ng/ml, p<0.001]. Surgery was 2.1 ± 2.3 days in group 1 and 2.0 ± 1.9 days in group 2 (p>0.05).

Predictive values and the ROC curves used for the strength of our study parameters have been shown with following figures and tables.

| Variables | Term birth (n=54) | Preterm birth (n=19) | p |
|---|------------------------|------------------------|-------------|
| Cervical length (mm) | 34 ± 7 | 24 ± 7 | < 0.0001*** |
| Prolactin (ng/mL) | 0.071 (0.065-0.084) | 0.121 (0.082-0.391) | < 0.0001*** |
| Vitronectin (ng/mL) | 16 (9-41) | 90 (78-98) | < 0.0001*** |
| Gestational duration by the time of examination (day) | 224 (202-230) | 225 (213-231) | =0.450 |
| Birth time (day) | 275 ± 7 | 242 ± 11 | < 0.0001*** |
| Birth weight (g-newborn) | 3304 ± 430 | 2371 ± 292 | < 0.0001*** |

*p < 0.05, ** p < 0.001, ***p < 0.0001
 ('significant, **highly significant, *** very highly significant)
 Cervical length, birth week-time, birth weight are shown as mean (X ± SD); prolactin, vitronectin and the week of examination are shown as median (25. percentile-75. percentile)

The predictive role of vitronectin was presented in Table 2. Positive predictive value for vitronectin (PPV) has been found as 78 %, negative predictive value has been found as 100 % and the accuracy ratio has been found as 91.8 %.

| Test Result | Preterm Birth | Term Birth | Total |
|-----------------|---------------|------------|-------|
| Vitronectin (+) | 19 | 6 | 25 |
| Vitronectin (-) | 0 | 48 | 48 |
| Total | 19 | 54 | 73 |

According to this, sensitivity has been found as 100 % and specificity has been found as 89 %. ROC curve area for vitronectin has been found as 0.96 and this is compatible with 'perfect' (Figure 1).

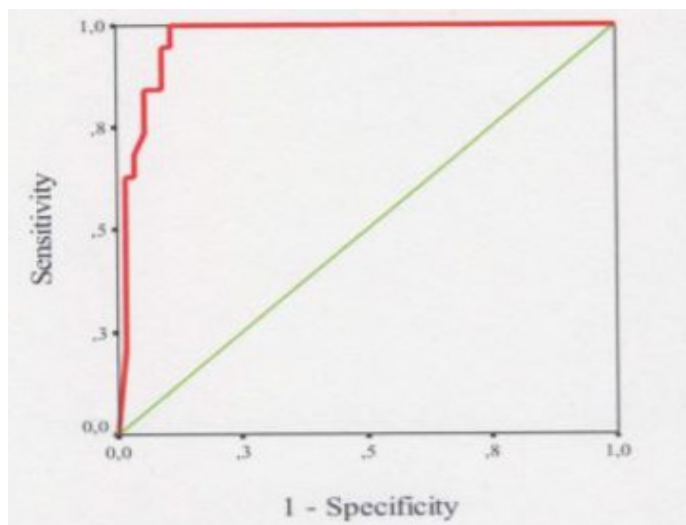


Figure 1. ROC curve for vitronectin.

None of the preterm births has vitronectin levels under the cut-off value, that's why 100 % for NPV has been obtained.

Average value for vitronectin levels have been found 26 ng/mL in pregnant who had term deliveries (n=54), and 87.7 ng/mL in pregnant who had preterm birth (n=19) (Figure 2).

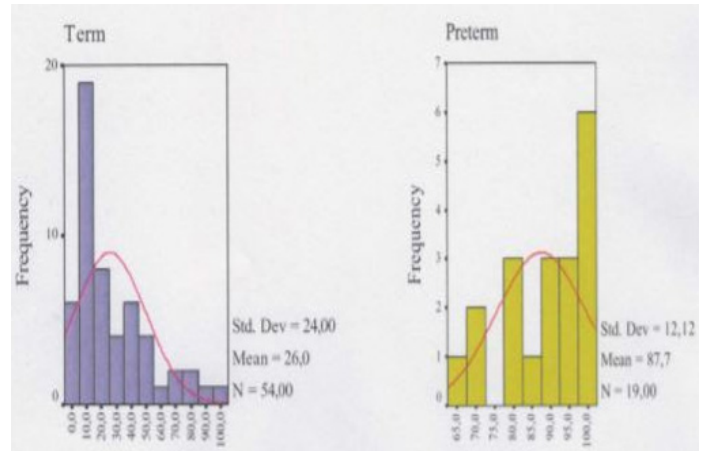


Figure 2. Histogram chart for the distribution of vitronectin value in term and preterm groups

Predictive value of prolactin was shown in Table 3. Positive predictive value for prolactin (PPV) has been found as 58.3 %, negative predictive value has been found as 89.8 % and the accuracy ratio has been found as 79.4 %. (Figure 3).

| Test Result | Preterm Birth | Term Birth | Total |
|---------------|---------------|------------|-------|
| Prolactin (+) | 14 | 10 | 24 |
| Prolactin (-) | 5 | 44 | 49 |
| Total | 19 | 54 | 73 |

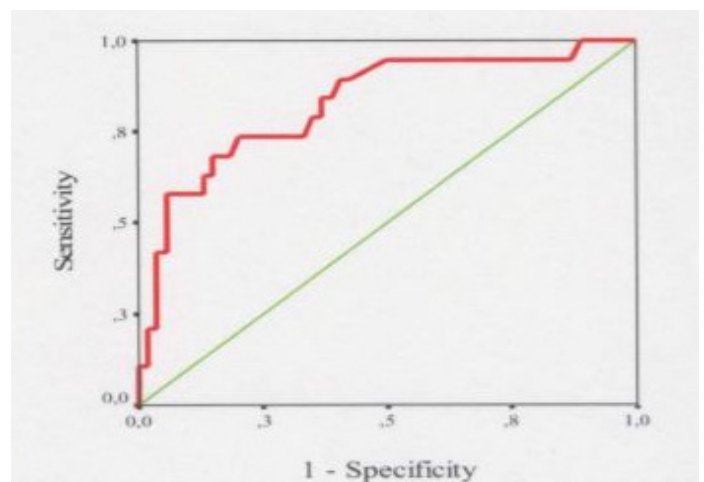


Figure 3. ROC curve for prolactin

Average value for prolactin levels have been found 0.14 ng/mL in pregnant who had term deliveries (n=54), and 2 ng/mL in pregnant who had preterm birth (n=19) (Figure 4) (Table 4).

Predictive value of cervical length was demonstrated in Table 4. Positive predictive value for cervical length (PPV) has been found as 51.5 %, negative predictive value has been found as 95 % and the accuracy ratio has been found as 75.3 %.

| Test Result | Preterm Birth | Term Birth | Total |
|-----------------------------------|---------------|------------|-------|
| Cervical length (≤ 31.5 mm) | 17 | 16 | 33 |
| Cervical length (≥ 31.5 mm) | 2 | 38 | 40 |
| Total | 19 | 54 | 73 |

Average value for cervical length have been found 34.5 mm in pregnant who had term deliveries (n=54), and 24.2 mm in pregnant who had preterm birth (n=19) (Figure 5, 6)

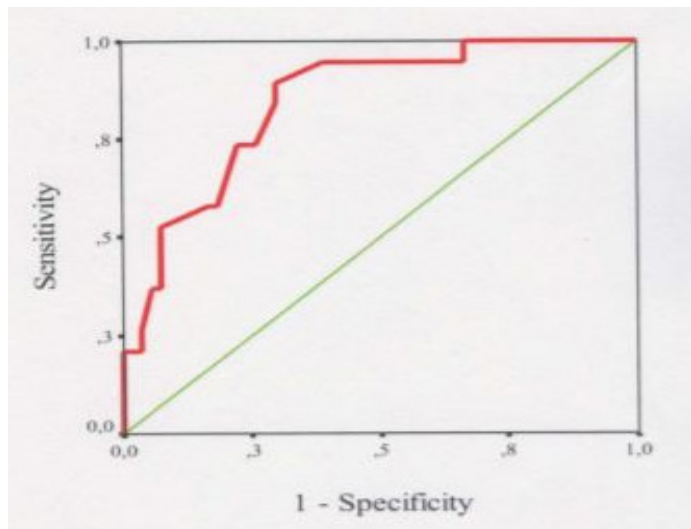


Figure 5. ROC curve for cervical length

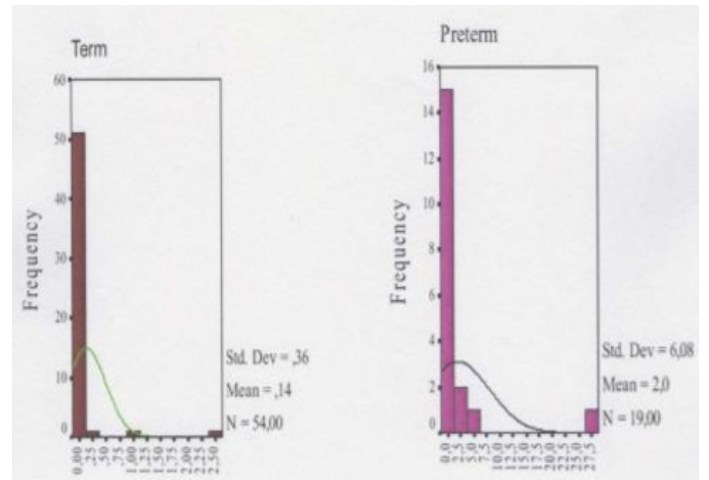


Figure 4. Histogram chart for the distribution of prolactin value in term and preterm groups

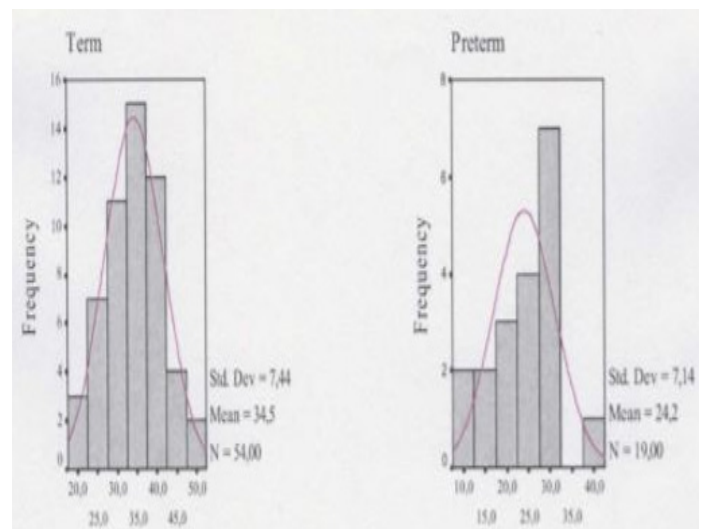


Figure 6. Histogram chart for the cervical length values in term and preterm groups

Spearman coefficient (r_s) has been used for vitronectin, prolactin and examination week. Pearson coefficient (r_p) has been used for cervical length, birth week and birth weight. According to the correlation analysis results,

vitronectin was strongly positively correlated with prolactin levels while it was negatively correlated with cervical length ($r = 0.691$ and $r = -0.348$ respectively) (Table 5).

| Examination week | Birth weight (g) | Birth week | Cervical length (mm) | Prolactin (ng/mL) | Vitronectin (ng/mL) |
|------------------|------------------|------------|----------------------|-------------------|---------------------|
| | | | | | 1 |
| | | | | 1 | 0.691** |
| | | | 1 | -0.456* | -0.348* |
| | | 1 | 0.541* | -0.310* | -0.234 |
| | 1 | 0.820*** | 0.495* | -0.328* | -0.251 |
| 1 | -0.055 | 0.011 | -0.505* | 0.438* | 0.006 |

*Spearman coefficient (r_s) has been used for vitronectin, prolactin and examination week. Pearson coefficient (r_p) has been used for cervical length, birth week and birth weight. *Significant, **highly significant, ***very highly significant

DISCUSSION

Preterm birth has been the most common cause of neonatal deaths independent from fetal anomalies with an incidence of 6-13 %. Also it has been an important health issue even in developed countries (3). Most of the deaths caused by preterm birth have been seen in neonates born before 30th week of gestation. Therefore many studies have been undertaken for prediction of the birth time accurately. It has been the target to find out if there is any possibility of a cervicovaginal marker for prediction of preterm birth. It has been an attractive issue to find out a marker that can classify the women which do not have risk for preterm birth, and so there would not be any necessity for repeated examination and staying in the hospital.

Guvenal and colleagues have studied prolactin levels in cervicovaginal secretions for the prediction of preterm birth (28). Both their and our studies have shown preterm birth, well. They have determined the cut off value as 1.8 ng/mL, and we have determined as 0.088 ng/mL. This difference could be explained by the difference of methods used for collecting samples. Since 10 pregnant women who had term delivery, also had higher prolactin levels than the cut-off value, the PPV has been found lower in our study.

There has been many studies about cervicovaginal fibronectin and cervical length. They have been studied separately or in combination. Cervical length measurement by TVUSG is a noninvasive method and gives objective information about preterm birth risk. Even if it has been used commonly there has not been any standardization of this measurement. Measurement technique, indications and the examination intervals have not been well defined. According to the suggestion of American College of Radiology, cervix and lower uterine segment should be visualized in every obstetric ultrasonography of 2nd trimester. Short cervix (< 30 mm) or funnelling should be investigated specially (29). Iams and colleagues have evaluated 2915 low risk, singleton pregnant women and while they have taken the cut-off for cervical length as 20 mm in 24th and 28th weeks, they have found sensitivity as 23 %, and specificity as 93%. If the cut-off value has taken as 25 mm, sensitivity has been found as 54 %, and specificity has been found as 92 % (16). The cut off value for cervical length in this study has been determined as 31.5 mm. According to this cut off value, sensitivity has been found as 70.3 %, specificity as 89.4 %, PPV 51.5 %, NPV 95 % and the area under ROC curve as 0.85. Cervical length under 25 mm, has been considered as significant for preterm birth, in the literature. As we take cut off value as 25 mm in this study, we have found sensitivity as 52.6 %, specificity as 92.5 %, PPV 71.4 %, NPV 84.7 % and the accuracy rate as 82.2%. As the cut off value has taken as 25 mm, sensitivity and NPV values decrease and PPV and accuracy rates increase. In the study of Iams and colleagues, only one of 147 patients, which all have negative fibronectin results, has preterm birth and this has shown that the NPV for fibronectin is 99.5 %. Results have shown that

fetal fibronectin levels have given more accurate results than uterine contractions and cervical dilatation for prediction of preterm birth (30). Gomez and colleagues have used fibronectin levels combined with cervical length measurement, and they suggested that this combination improves diagnostic accuracy (31). Meta-analysis has shown that negative fibronectin level is a strong marker for that the preterm birth will have not been occurred in 7-10 days period (32,33).

Studies with prolactin and fibronectin have caused to consider if there could be any other markers to predict preterm birth accurately and in time. So we studied vitronectin, a matrix glycoprotein, for this aim. Until now, we have not seen any study about preterm delivery and vitronectin relation in the literature. That's why this should be the first findings about this relation. None of the preterm births in our study has showed vitronectin levels under the cut off value, so NPV has been found as 100 %. Besides any pregnant with negative vitronectin did not have preterm birth.

In study design patients are chosen randomly not dependent to existence of symptoms, therefore examination and sample collecting have been done in random weeks of the applicance. This estimates that the examination day and the sample recruitment time have been standardized and that makes the results of the study countable and valuable. The prediction has been independent from the week, it can be predicted in early weeks of gestation far earlier than the symptoms begin. For this evaluation advanced statistical analysis and large scale population studies could be designed. In the connective tissue of gum, there has been vitronectin with fibronectin, spreadly (34). It can be another query to investigate high preterm birth risk in periodontal diseases for investigation. As far as it could be understood, vitronectin could be a mediator in cell migration of inflammatory cells to the media (neutrophile and endothelial cell migration and vitronectin relation have been reported). Besides, calcium metabolism has been necessary for uterine contraction and this molecular pathway has been a target for treatment. Calcium mediates the intracellular effect of vitronectin, as well. Calcium channels blockers have already been used in the management of preterm birth (35).

There has been some trials those detected relation in between vitronectin and preeclampsia. It has been studied in early diagnosis of preeclampsia and also studied with some coagulation cascade members (36-38).

Whatever the cause of preterm birth exists, all effective mechanisms activate the pathways resulted in secretion of inflammatory mediators and vitronectin seems to be placed in all of these processes. For instance, the actual clinical treatment of central nervous system tumors (glioma), antibodies against receptors those vitronectin binds has been used and that strategy could have prevented the tumoral invasion. Some other trials have reported the successful prevention of neovascularization and tumor progression (39, 40). Brand new strategies could have been used to blockade the migration of inflammatory

trigger cells in preterm birth.

CONCLUSION

It can be an optimum management to find out the marker specialized for the risk factor of preterm birth, but a common, direct marker like vitronectin would be an independent, countable marker in the diagnosis of preterm birth. Besides it would be very useful to determine which pregnant would not have preterm birth and it would be doing this independent from the gestational week, as well so there would be no necessity to stay in hospital for days. Maybe in the future, these kinds of markers would be the criteria for hospitalization. By this triage, both time loss in diagnosis and treatment would be prevented and the cost of management would be diminished. There has not been any study about vitronectin and preterm birth relation in the literature as we searched by now and this makes our study important for this area of the literature. The other significance of this study is that the predictions are independent from the gestational week so it can be predicted far before the symptoms occur.

In the light of these findings, vitronectin could be a valuable marker for preterm birth risk confirmation. There has not been any cause and effect relation, yet but there should be more studies done to make clear the relationship between vitronectin and many other molecules like integrins in its microenvironment. If these interactions have been understood well, the diagnosis, the management and the treatment strategies will be better timed and well directed.

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Ebru İnci Coskun ORCID: 0000-0003-4402-3725

Salim Sezer ORCID: 0000-0003-1287-4306

Ismail Dag ORCID: 0000-0002-9432-7965

Ercan Yilmaz ORCID: 0000-0003-3821-4621

Yavuz Tahsin Ayanoglu ORCID: 0000-0002-1605-3620

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