PERINATAL JOURNAL

Original Article

Perinatal Journal 2016;24(2):77–82

Evaluation of the measurement of ACTH, fibronectin, pentraxin 3 levels and cervical length in pregnant women under threatened preterm delivery

Filiz Aktenk[1], Burcu Artunç Ülkümen[2], Yeşim Güvenç[3], Halil Gürsoy Pala[2], Arzu Oran[3]

[1]Gynecology and Obstetrics Clinic, Cizre State Hospital, Mardin, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[3]Department of Biochemistry, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

Abstract

Objective: We aimed to compare ACTH, fibronectin and pentraxin 3 levels and cervical lengths in pregnant women under the risk of threatened preterm delivery with the levels in non-complicated normal pregnant women, to determine the significance of these markers on the threatened preterm delivery and to establish new markers which can be used as risk factors.

Methods: Thirty healthy pregnant women and 30 pregnant women established the diagnosis of the threatened preterm delivery who were between 18 and 40 years old and at 24–34 weeks of gestation and admitted to the Department of Obstetrics and Gynecology, Faculty of Medicine, Celal Bayar University were included in the study. Age, educational level, height/weight measurements, number of pregnancy, parity, smoking habit, presence of systemic disease and previous pregnancy histories were reviewed. Cervical length of all pregnant women participated in the study were measured by transvaginal sonography. After venous blood samples were collected, ACTH, fibronectin and pentraxin 3 levels were studied. The results were compared statistically in both groups via SPSS-20.

Results: In our study, the preterm delivery incidence was 27.1%. The rate of pregnant women, who had preterm delivery, to the study group was 53.3%. When the data of study and control groups were compared, no significant difference was found in terms of sociodemographic characteristics ($p>0.05$). While mean cervical length in the study group was 17.56 mm, it was found as 44.74 mm in the control group, and the difference was considered as statistically significant ($p<0.001$). ACTH and fibronectin levels were compared in the data of study and control groups and the difference was not found to be statistically significant ($p>0.05$). While mean pentraxin 3 level in the study group was 35.83 pg/mL, it was found as 20.26 pg/mL in the control group, and the difference was considered as statistically significant ($p<0.001$).

Conclusion: We believe that pentraxin 3 as a new acute phase reactant can be used as a marker to establish the diagnosis of threatened preterm delivery or to support the diagnosis.

Keywords: ACTH, cervical length measurement, fibronectin, pentraxin 3, threatened preterm delivery.

Özet: Erken doğum tehdidi olan gebelerde ACTH, fibronektin, pentraksin 3 düzeyleri ve servikal uzunluk ölçümlerinin değerlendirilmesi

Amaç: Erken doğum tehdidi olan gebelerde ACTH, fibronektin, pentraksin 3 düzeyleri ve servikal uzunluğu, komplike olmayan normal gebelerdeki düzeyleri ile karşılaştırarak bu belirteçlerin erken doğum tehdidi üzerindeki önemini belirlemek ve risk faktörü olarak kullanılabilecek yeni belirteçler oluşturabilmek amaçlanmıştır.

Yöntem: Çalışmaya Celal Bayar Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'na başvuran 18–40 yaş arası, 24–34 hafta arasında sağlıklı 30 gebe ve erken doğum tehdidi tanısı almış 30 gebe dahil edildi. Gebelerin yaş, eğitim düzeyi, boy/kilo ölçümleri, gebelik sayısı, paritesi, sigara kullanma alışkanlığı, sistemik hastalık varlığı, önceki gebelik öyküleri sorgulandı. Çalışmaya katılan tüm gebelerde transvajinal sonografi ile servikal uzunluk ölçümü yapıldı. Venöz kan örnekleri alındıktan sonra ACTH, fibronektin ve pentraksin 3 düzeyleri çalışıldı. Sonuçlar her iki grupta SPSS-20 programında istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmamızda preterm eylem sıklığı %27.1 olarak saptandı. Preterm eylem gerçekleşen gebelerin çalışma grubuna oranlarının ise %53.3 olduğu görüldü. Çalışmaya alınan gebelerde çalışma ve kontrol grupları verileri karşılaştırıldığında sosyodemografik özellikler yönü ile anlamlı farklılık izlenmedi ($p>0.05$). Çalışma grubunda yer alan gebelerde ortalama serviks uzunluğu 17.56 mm iken kontrol grubunda ortalama değer 44.74 mm saptandı ve aradaki fark istatistiksel olarak anlamlı bulundu ($p<0.001$). Çalışma ve kontrol grubu verilerinde karşılaştırılan ACTH ve fibronektin düzeyleri arasında istatistiksel olarak anlamlı farklılık izlenmedi ($p>0.05$). Pentraksin 3 düzeyleri karşılaştırıldığında çalışma grubunda ortalama değer 35.83 pg/mL iken, kontrol grubunda 20.26 pg/mL saptandı ve aradaki fark istatistiksel olarak anlamlı bulundu ($p<0.001$).

Sonuç: Yeni bir akut faz reaktanı olan pentraksin 3'ün erken doğum tehdidi tanısı koymada veya tanıyı desteklemede kullanılabilecek bir belirteç olabileceği düşüncesindeyiz.

Anahtar sözcükler: Erken doğum tehdidi, servikal uzunluk ölçümü, ACTH, fibronektin, pentraksin 3.

Correspondence: Burcu Artunç Ülkümen, MD. Celal Bayar Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Manisa, Turkey. e-mail: artunc.burcu@gmail.com

Received: March 18, 2016; **Accepted:** June 6, 2016

Please cite this article as: Aktenk F, Artunç Ülkümen B, Güvenç Y, Gürsoy Pala H, Oran A. Evaluation of the measurement of ACTH, fibronectin, pentraxin 3 levels and cervical length in pregnant women under threatened preterm delivery. Perinatal Journal 2016;24(2):77–82.

Available online at:
www.perinataljournal.com/20160242004
doi:10.2399/prn.16.0242004
QR (Quick Response) Code:

deomed

Introduction

Preterm delivery is the condition of frequent and active uterine contraction causing cervical effacement and dilatation during 20–37 weeks of gestation. Threatened preterm delivery is the condition of regular uterine contraction beginning before 37 weeks of gestation and causing no change in the cervix. Preterm delivery is a serious obstetric problem today with the high perinatal mortality and morbidity rates caused by preterm delivery it cause.[1] Despite the efforts to prevent preterm delivery, desired results cannot be always achieved due to the difficulties to understand the underlying pathophysiology, insufficient diagnosis methods.[2] Therefore, the most effective solution to find is to identify risky pregnant women under risk in the appropriate time and to decrease risk factors for such pregnant women who are candidate for preterm delivery.

Adrenocorticotrophic hormone (ACTH) is a hormone in polypeptide structure with straight chain containing 39 aminoacid. Other substances secreted by hypothalamus such as arginine vasoporessine (AVP) also stimulate ACTH release more weakly and probably this effect also depends on the presence of corticotrophin releasing hormone (CRH). ACTH increase in the circulation causes glucocorticoid secretion from adrenal cortex (cortisol in human). In response to the maternal or fetal stress, the activation of hypothalamic-hypophyseal-adrenal axis is responsible for 30% of preterm delivery. Physical or psychological stress of mother and placenta dysfunctions increases uteroplacental CRH secretion. CRH increases ACTH secretion from hypophysis. As a result, cortisol secretion in fetal and maternal adrenals increases.[3] This causes prostaglandin production. With direct uterotonic effect, prostaglandines activates myometrium by increasing oxytocin receptors in myometrium and the formation of gap junction.[4] It may lead to myometrial contractions and cervical changes. It is also considered that myometrium activation, namely delivery, is activated with the increased release of CRH, as if a placental clock is programmed, and with the increased release of ACTH from fetal pituitary gland and therefore the production of placental estrogenic components.[5]

Preterm delivery is responsible for 40% of the reasons of infection and inflammation although it has a multifactorial etiology. Pentraxin 3 (PTX3) is a new acute phase marker similar to C-reactive protein in terms of structure and function. As a result of inflammation, it is released from liver, endothelium cells, atherosclerotic lesions, macrophage and neutrophiles.[6] Detection of the increase in this inflammation marker may have a role to determine inflammation and preterm delivery that may develop due to inflammation.[7,8]

Fibronectin is a dimeric glycoprotein with the molecular weight of 440,000 Dalton. It has a role in the adhesion of cell-cell and cell-substrate, adherence of fibrinogen or collagen to macrophage and fibrin clot retraction of fibroblasts, and it regulates cell movements. It also helps the continuation of microvascular integrity, control of vascular permeability, hemostasis and wound healing.[9,10] Plasma fibronectin level during pregnancy increases for 20% at third trimester and stays at this level for postpartum 6 weeks. Renal and hypertensive diseases, diabetes mellitus, surgical operation during pregnancy and blood transfusion, coagulation disorders, premature rupture of membrane and chorioamnionitis may cause changes in plasma fibronectin level.[11,12] It is considered that preterm delivery can be identified with the detection of this factor, with increasing mechanical or inflammatory post-trauma release. In a study carried out, it was found that incidence rate of preterm delivery is 70% in case that fibronectin level increases.[12]

In this study, we aimed to compare ACTH, fibronectin and PTX3 levels and cervical lengths in pregnant women under the risk of threatened preterm delivery with the levels in non-complicated normal pregnant women, to determine the significance of these markers on the threatened preterm delivery and to establish new markers which can be used as risk factors.

Methods

Our study was a randomized prospective study conducted on a total of 60 pregnant women, including 30 pregnant women (study group) between 24 and 34 weeks of gestation who were established the diagnosis of threatened preterm delivery at the Gynecology and Obstetrics Department of Hafsa Sultan Hospital, Celal Bayar University and 30 pregnant women (control group) admitted for routine follow-up to the Pregnancy Clinic of Gynecology and Obstetrics Department during the same weeks of gestation between December 2013 and January 2015.

Pelvic examination was applied first to the patients who admitted to our hospital with the complaints such as the feelings of contraction, stiffening and pelvic pres-

sure in the abdomen, increased vaginal discharge and cramps similar to those during menstruation. With USG, fetal biometry and amniotic fluid amount were measured. The presence of active and regular uterine contractions was sought with external tocodynamometer. Gestational age identification was done by confirming with the first trimester ultrasonography according to last menstrual period and with the ultrasonography in those with unknown last menstrual period.

While the bladder was empty on lithotomy position in 60 pregnant women included in the study, sagittal image of the cervix was obtained with 5 mHz and 120 degree convex-angle vaginal probe in a sterile way by applying lubricant gel and placing condom to the probe and by avoiding to make any pressure to the cervix. Cervical measurements were done in a cross-section, where also internal os, external os, cervical canal and endocervical mucosa could be displayed, by enlarging the image as covering 3/4 of the screen. Also, in cases where the length between internal os and external os was not on a single line, they were measured as linear sections and total cervical length was obtained by summing up them. Any funneling in internal os, which is 5 mm and above, was recorded.

When establishing preterm delivery diagnosis, the presence of regular and active (45–50 mmHg) uterus contractions which were 4 times per 20 min. or 6 times per 60 min. as well as the presence of any of the cervical changes during ≥2 cm cervical opening or observation were considered as the criteria. The patients having effacement or opening without any uterine contradiction were considered to have cervical failure and excluded from the study. The pregnancies with ≥4 cm cervical opening, ≥80% effacement, had previous premature rupture of membrane, severe preeclampsia-eclampsia, ablatio placentae, placenta previa, chorioamnionitis, IUGR, dead fetus, fetal anomaly incompatible with life, and multiple pregnancy were excluded from the study.

The heights and weights of pregnant women who were included in our study were measured in the beginning of their pregnancies and at the week they were included in the study.

The venous bloods collected from the pregnant women in the study and control groups between 08:00 and 10:00 a.m. following the nocturnal fasting were centrifuged at 4000 rpm for 15 min. at +4°C. The serums were separated into Eppendorf tubes and were kept at deep freeze at -80 °C until analysis time.

Fibronectin levels were measured with ELISA method by using the commercial kit (Affymetrix, eBioscience, Vienna, Austria). The kit sensitivity was 0.1 ng/mL, intra-assay CV was 5.3% and inter-assay CV was 6.7%.

Pentraxin 3 levels were measured with ELISA method by using the commercial kit (R&D Systems, Minneapolis, MN, USA). The kit sensitivity was 0.025 ng/mL, intra-assay CV was 3.93% and inter-assay CV was 5.06%.

For the study, the approval of Ethics Board of Hafsa Sultan Hospital, Celal Bayar University, the pregnant women to be included in the study were informed about the study and consent forms were signed by the patients.

The data obtained from the study were entered into the database created in SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA) and the statistical analyses of the data were done in the same software. Mean, standard deviation, median, minimum and maximum values of constant variables and their subgroups, and frequency numbers and percentages of class variables were presented. "Independent samples t-test" method was used in the comparison of independent variables consistent with normal distribution while "Mann-Whitney U" test was used for the comparison of independent group inconsistent with normal distribution. Class variables were presented as frequency and percentages in cross tables and their distributions were compared with "chi-square" test methods. In all tests, 1st type error margin alpha was considered as 0.05 and they were tested in two way; the difference between the groups was considered to be statistically significant when p value was lower than 0.05.

Results

These four parameters were compared in the data of the study group consisting of pregnant women diagnosed with the threatened preterm delivery and followed-up by hospitalizing and the control group consisting of pregnant women admitted to our Gynecology and Obstetrics Clinic for routine check and gestational follow-up; the mean cervical length was measured as 17.56±7.90 mm in the study group and as 44.74±3.23 mm in the control group, and the difference was found statistically significant ($p<0.001$).

In terms of fibronectin levels, the mean value was 116.18±58.36 mg/L in the study group and 99.74±47.47

mg/L in the control group, but the difference was not considered as statistically significant (p>0.05). Similarly, mean ACTH level was found to be 26.49±14.48 pg/mL in the study group and 28.41±15.26 pg/mL in the control group, but the difference was not considered as statistically significant (p>0.05).

When mean PTX3 levels, as the new acute phase reactant, were compared in both groups, it was found as 35.83±2.17 pg/mL in the study group and as 20.26±1.72 in the control group, and the difference was considered as statistically significant (p<0.001) (**Fig. 1**).

In our study, we found preterm delivery incidence as 27.1%. The rate of pregnant women, who had preterm delivery, to the study group was 50%.

Pregnant women in the study group who were diagnosed with the threatened preterm delivery were separated into two groups according to the incidence of preterm delivery. According to this, Group I included pregnant women who were diagnosed with the threatened preterm delivery and had the preterm delivery afterwards and Group II included pregnant women who were diagnosed with the threatened preterm delivery but delivered at term. Cervical length, fibronectin, ACTH and PTX3 measurements of Group I and Group II were compared and it was found that there was statistically significant difference in cervical length and PTX3 levels compared to the control group (p>0.001) while there was no statistically significant difference between Group I and Group II (p>0.05).

Discussion

With the improvement of newborn care opportunities and significant improvement in the prognosis of babies with low birth weight, nursling, neonatal and postnatal mortality rates decreased about by half in the last two decades. However, the mortality rates did not decrease in preterm (<37 weeks) deliveries and newborns with low birth weight (LWB <2500 g).[13]

Preterm delivery and low birth weight are the most significant factors affecting perinatal mortality and morbidity in the modern obstetrics, and their improvement will enhance the general health of the society. As preterm delivery depends on many reasons, its actual mechanism is still unknown despite many studies. Therefore, protection, early diagnosis and treatment of preterm delivery have been significant problems in perinatal medicine.[14]

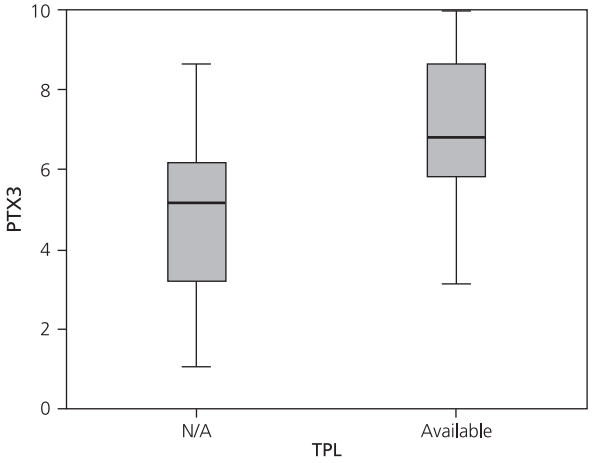

Fig. 1. Pentraxin 3 (PTX3) levels in pregnant women with the threatened preterm delivery (TPD).

Although it is known that the activation of hypothalamic-hypophyseal-adrenal axis is responsible for 30% of preterm delivery in response to the maternal or fetal stress, ACTH levels of study and control groups checked between 08:00 and 10:00 a.m. showed no statistically significant difference (p>0.05). It was thought that this result was obtained due to time differences in collecting serum samples, problems for maintaining cold chain that may occur during the transfer of samples to the laboratory, seasonal changes, maternal response to psychological stress, and the difference in cortisol response of maternal and fetal adrenals. In order to obtain significant results, it is required to improve study conditions, and to carry out a study with more population by using serum samples taken simultaneously from more pregnant women chosen from a group with particular demographic and physical characteristics.

In terms of the distribution among etiological factors, it is seen that 80% of the preterm deliveries are caused by spontaneous preterm delivery and preterm premature rupture of membrane (PPROM), and 20% of them are caused by maternal and fetal problems.[15]

The recent studies support the role of infection in the etiology of preterm delivery. The role of subclinical infection in placental membranes, chorioamnionitis occurring before and after chorioamniotic membranes are opened and histological infection gain importance in the etiology.[1,13,15] Microorganisms were isolated for 2–4 times more in the placental membranes of preg-

nant women who had preterm delivery compared to the pregnant women who delivered at term.[13]

Identifying and treating maternal infection has an increasing importance in order to decrease preterm deliveries and avoid neonatal outcomes of prematurity. Infection markers such as C-reactive protein, alkaline phosphatase, beta-2 microglobulin, alpha-2 macroglobulin, serum leucocyte count and shift to left in the formula are used to investigate maternal infection and inflammatory.

In our study for these findings, we compared fibronectin and PTX3 levels as an acute phase reactant in pregnant women with and without the threatened preterm delivery and cervical length measurement, which is proven for its validity and significance in many studies, as another parameter in patients with the threatened preterm delivery.

Despite the frequent use of cervical length measurement in the diagnosis of threatened preterm delivery, no standardization, technique, indications and examination ranges have been determined for the measurements. According to the recommendation of American College of Radiology, cervix and lower uterine segment should be displayed in each second trimester obstetric ultrasonography. Specifically, the presence of short cervix (<30 mm) or funneling should be investigated.[16] Iams et al. investigated 2915 low-risk singleton pregnancies between 24 and 28 weeks to determine deliveries before 35 weeks of gestation and found the sensitivity as 23% and the specificity as 93% when the threshold value of cervical length measurement was taken as 20 mm, the sensitivity as 54% and the specificity as 92% when the threshold value was taken as 25 mm and the sensitivity as 25% and the specificity as 95% when the threshold was taken as 30 mm. In the same study, they reported that preterm delivery before 35 weeks of gestation increased 6 and 9 times, respectively, when the cervical length measurement was below 26 mm.[17] It is known that cervical length measured between 18 and 22 weeks of gestation in asymptomatic patients is important in the prediction of preterm delivery.[18]

There was no statistically significant difference between the fibronectin levels of the pregnant women diagnosed with the threatened preterm delivery (mean value was 28.08 mg/L) and the fibronectin levels of the pregnant women without the threatened preterm delivery (mean value was 29.02 mg/L) ($p>0.05$). The reasons of this result were considered that many types of fibronectin in different forms suppress especially apoptosis in embryogenesis, it is known that it affects hemopoietic precursor cell maturation and differentiation, it controls signal transfer between the cells and it has low sensitivity and specificity to inflammatory process occurring in the threatened preterm delivery depending on the fact its main production site is hepatocytes although it is produced in many cells.[19]

In previous studies, oxidative stress markers were investigated within amniotic fluid for the prediction of preterm delivery; however, no significant result was found.[20] It was reported that maternal serum d-dimer levels might be useful in the prediction of preterm delivery.[21] PTX3 values which are inflammatory markers are normally quite low in the plasma. However, it increases very quickly in inflammatory diseases, degenerative diseases and autoimmune disorders. This increase is directly proportional to the weight of patient. In our study, we found increase in PTX3 levels of pregnant women diagnosed with the threatened preterm delivery compared to the control group. While the mean value was 35.83 pg/mL in the study group, it was 20.26 pg/mL in the control group. Also when PTX3 levels of the pregnant women in the study group who had preterm delivery were compared with the pregnant women in the control group, the mean PTX3 level in the pregnant women who had preterm delivery was found as 37.75 pg/mL and the difference among them were considered as statistically significant ($p<0.001$). Absence of premature rupture of membrane in the pregnant women included in the study group rules out the suspicion that the increase in PTX3 levels may occur as a result of inflammatory reaction developing due to a possible chorioamnionitis.

Conclusion

The high PTX3 levels were statistically significant in pregnant women who were diagnosed with the threatened preterm delivery and whose diagnoses were supported with the shortening cervical lengths. Accordingly, we believe that pentraxin 3 as a new acute phase reactant can be used as a marker to establish the diagnosis of threatened preterm delivery or to support the diagnosis. Therefore, further studies at larger scales are required.

Conflicts of Interest: No conflicts declared.

References

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams obstetrics. 22nd ed. New York, NY: McGraw-Hill Co; 2005. Chapter 36, Preterm birth. p. 855–80.
2. Mc Donald HM, O'loghlin JA, Jolley P, Vigneswaran R, McDonald PJ. Prenatal microbiological risk factors associated preterm birth. Br J Obstet Gynaecol 1992:99:190–6.
3. Şener T. Preterm eylem ve doğum. In: Kişnişçi H, Gökşin E, Durukan T, Üstay K, Ayhan A, Gürkan T, Önderoğlu L, editors. Temel kadın hastalıkları ve doğum bilgisi. Ankara: Güneş Kitabevi; 1996. p. 1465–80.
4. Hein M, Petersen AC, Helmig RB, Uldbjerg N, Reinholdt J. Immunoglobulin levels and phagocytes in the cervical mucus plug at term of pregnancy. Acta Obstet Gynecol Scand 2005;84:734–42.
5. Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325:669–74.
6. Salio M, Chimenti S, De Angelis N, Molla F, Maina V, Nebuloni M, et al. Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. Circulation 2008;117:1055–64.
7. Mantovani A, Garlanda C, Bottazzi B, Peri G, Doni A, Martinez de la Torre Y, et al. The long pentraxin PTX3 in vascular pathology. Vascul Pharmacol 2006;45:326–30.
8. Mantovani A, Garlanda C, Bottazzi B. Pentraxin 3, a non-redundant soluble pattern recognition receptor involved in innate immunity. Vaccine 2003;21 Suppl 2:S43–7.
9. Mosesson MW, Amrani DL. The structure and biological activites of plasma fibronectin. Blood 1980;56:145–58.
10. Mosher DF. Physiology of fibronectin. Annu Rev Med 1984;35:561–75.
11. Stubbs TM, Lazarchick J, Horger EO 3rd. Plazma fibronectin levels in preeklampsia: a possible biochemical marker for vasculer endhotelial damage. Am J Obstet Gynecol 1984;150: 885–7.
12. O'Brien WF. Predicting preeklampsia. Obstet Gynecol 1990; 75:445–52.
13. Creasy RK, Iams JD. Preterm labor and delivery. Creasy RK, Resnik R. In: Maternal-fetal medicine. 4th ed. Philedelphia, PA: WB Saunders Company; 1999. p. 498– 531.
14. Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: Final data for 2000. Natl Vital Stat Rep 2001;50:1–119.
15. Creasy RK, Merkatz IR. Preventation of preterm birth: clinical opinion. Obstet Gynecol 1990;76(1 Suppl):2S–4S.
16. Mantovani A, Garlanda C, Bottazzi B, Peri G, Doni A, Martinez de la Torre Y, et al. The long pentraxin PTX3 in vascular pathology. Vascul Pharmacol 2006;45:326–30.
17. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous preterm delivery. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. N Engl J Med 1996;334:5675–72.
18. Arısoy R, Erdoğdu E, Tuğrul S, Mirza T, Fındık F, Mihmanlı M, et al. Düşük riskli asemptomatik gebeliklerde erken doğum tahmininde gebeliğin 18-22. haftalarında servikal uzunluk ölçümü. Perinatoloji Dergisi 2013;21(Suppl):25.
19. Foix-L'Helias L, Ancel PY, Blondel B. Risk factors for prematurity in France and comparsons between spontaneous prematurity and induced labor: results from The National Perinatal Survey 1995. [Article in French] J Gynecol Obstet Biol Reprod (Paris) 2000;29:55–65.
20. Çelik E, Karaer A, Yılmaz E, Türkçüoğlu I, Çelik Ö, Şişmşek Y, et al. Investigation of the relationship between levels of oxidative stress markers in the second trimester amniotic fluid with preeclampsia and preterm delivery. Perinatal Journal 2012;20:140–5.
21. Yazıcıoğlu F, Oran R, Özsoy B, Aygün M, Özyurt ON, Demirbaş R, et al. The role of uterine artery doppler and maternal serum d-dimer levels in prediction of preterm labor. Perinatal Journal 2007;15:99–107.