# MsAFP As a Predictive Determinant in Preterm Labor

## *PRETERM EYLEMDE PREDİKTİF BELİRLEYİCİ OLARAK MsAFP*

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## Summary

**Objective:** Preterm labor is a problem that cannot effectively be solved by recent treatment methods and is responsible from 75-83% of infant mortality and morbidity. Thus, the importance of predictive determinants increases day by day. Although there are some available predictors with high sensitivity and specificity, maternal serum alpha-fetoprotein (MsAFP) is a relatively cheap and feasible method. In this study we aimed to establish the reliability of this method.

**Material and methods:** 120 patients hospitalized with the diagnosis of preterm labor and 110 patients (the control group) whose monthly controls were completed at our antenatal outpatient clinic were included in this study. The statistical analyses were performed with SPSS for Windows version 9.0, by using the Chi-Square test, one-way variance analyses, Bonferron test, Student's test, Pearson correlation analysis, and ROC analysis. The minimum limit for significance was taken as 0.05.

**Results:** The distribution of pregnancies was in between 32-37 gestational weeks. When the MsAFP concentrations were compared, the mean MsAFP level of 86 patients who were diagnosed to have preterm labor and who gave birth were statistically and significantly higher than both the control group and the patients diagnosed to have preterm labor who did not give birth. There was no significant difference in between the control group and the patients diagnosed to have preterm labor and who did not give birth. For the 32-37$^{th}$ weeks of gestation, the cut-off value was 106.05 ng/ml. Specificity was 70% for this value, sensitivity was 81.4% for the patients diagnosed to have preterm labor and who gave birth, 55.9 % for the patients diagnosed to have preterm labor and who did not give birth.

**Conclusion:** MsAFP elevation can be used as a predictor of preterm labor. However, this parameter needs to be evaluated in large patient populations and the cut-off value should be established.

**Key Words:** Preterm labor, MsAFP

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## Özet

**Amaç:** Güncel tedavi metodları ile etkin bir çözüm sağlayamadığımız preterm eylem, infant mortalitesi ve morbiditesinin %75-83'ünden sorumludur. Bu sebeple prediktif belirleyicilerin önemi, gün geçtikçe artmaktadır. Halihazırda sensitivitesi ve spesifitesi yüksek belli başlı belirleyiciler bulunmakla beraber, nispeten daha ucuz ve daha kolay sonuç verebilen bir yöntem olarak maternal serum alpha-fetoprotein (MsAFP) taramasının güvenirliğini bu çalışmamızda saptamayı amaçladık.

**Gereç ve yöntemler:** Preterm eylem tanısı ile hastanemize yatan 120 hasta ile, gebe polikliniğinde aylık muayenesini tamamlayan 110 hasta (kontrol grubu olarak) çalışmamıza dahil edildi. İstatistiksel değerlendirmeler SPSS for Windows version 9.0'da, Ki-Kare testi, tek yönlü varyans analizi, Bonferron testi, Student's t testi, Pearson momentler çarpımı, korelasyon analizi, ROC analizi kullanıldı. En küçük anlamlılık sınırı 0.05 olarak alındı.

**Bulgular:** Hastaların dağılım aralığı 32-37 hafta arasındaydı. MsAFP seviyeleri açısından karşılaştırıldığında, preterm eylem tanısı alıp doğuran 86 hastada ortalama MsAFP seviyesi, kontrol ve preterm eylem/doğurmayan gruplarına göre anlamlı olarak yüksek bulundu. Kontrol ve preterm eylem/doğurmayan grupları arasında anlamlı fark bulunmadı. 32-37 hafta arası için cut-off değer olarak 106.05 ng/ml sınır alındı. Spesifisite bu değer için %70, sensitivite preterm eylem/doğuran grupta %81.4, preterm eylem/doğurmayanlarda %55.9 idi.

**Sonuç:** MSAFP yüksekliği, erken doğum eyleminin prediktörlerinden biri olarak kullanılabilir. Ancak üzerinde hala geniş populasyonlarda çalışılması ve cut-off değeri tespit edilmesi gereken bir konu durumundadır.

**Anahtar Kelimeler:** Preterm eylem, MsAFP

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The incidence of preterm labor and preterm delivery is reported as 8-10% (1). This pathology carries the major responsibility in infant mortality and morbidity. Recent treatment modalities could not bring an effective solution to this problem. Thus determining the risk group and obtaining the continuation of pregnancy by close monitorization are extremely important. One of the predictors investigated for this reason is MsAFP. AFP is a glycoprotein similar in molecular weight and structure to albumin made first in the fetal yolk sac and then primarily in the fetal liver. AFP enters the amniotic fluid largely via fetal urination after renal filtration. Amniotic fluid AFP rises until approximately 12 weeks and there after declines. In contrast to fetal AFP, MsAFP continues to rise until 30-32 weeks before declining (2). Some authors reported that in pregnancies with idiopathic MsAFP elevation, the rate of complications like intrauterine growth retardation and preterm labor are higher when compared with the pregnancies in whom the MsAFP level is normal according to the gestational weeks (3). Thus, in this study we investigated the reliability of idiopathic MsAFP elevation.

## Material and Methods

In between 31 March 2001 and 31 December 2001, 120 patients hospitalized at our high risk pregnancy clinic with preterm labor (group 1) and 110 control patients applying to our antenatal outpatient clinic for routine pregnancy examination (group 2) were included in our study. Both patient groups were inquired about congenital diseases and chromosome abnormalities for both themselves and their families. History of systemic diseases, history of gestational diabetes in the current pregnancy and in previous pregnancies, habitual abortus, intrauterine growth retardation, preeclampsia, history of bleeding in the first trimester was inquired in both patient groups. Fetal abnormalities were ruled out with secondary care obstetric ultrasound and the current hemoglobin levels were recorded in the forms of patients. The criteria for preterm labor were at least two efficient contractions in ten minutes, cervical effacement and dilatation, and progression in the Bishop scores **in six hours**. Patients diagnosed to have intrauterine growth retardation, polihydramnios, oligohydramnios, multiple pregnancy, placenta previa, abruption placenta, preeclampsia, uterine abnormalities, systemic diseases, urinary infections, and chorioamnionitis were excluded from the study. 5 cc of venous blood was taken from the antecubital vein of each patient; the serum was separated and frozen. On the day of processing, all sera was brought to the room temperature and AFP levels were measured by the Irma-AFP radim kit and gamma-counter device. The statistical analyses were performed with SPSS for Windows version 9.0, by using the Chi-Square test, one way variance analyses, Bonferron test, Student's t test, Pearson correlation analysis, and ROC analysis. The minimum limit for significance was taken as 0.05.

## Results

The mean MsAFP level was 137.5 ± 59.2 ng/ml in Group 1 and 84.2 ± 45.6 ng/ml in Group 2 ($p<0.001$). The cut-off value was calculated as 106.0.5ng/ml with ROC analyses (Table 1).

Furthermore, the number of patients with MsAFP levels higher than the cut-off value was higher in the preterm/giving birth subgroup, when compared with both the preterm/not giving birth subgroup and the control group ($p<0.001$) (Table 2). There was no significant difference in between the control group and the preterm/not giving birth subgroup ($p>0.05$). The specificity for the cut-off 106.05 ng/ml value was 70%, the sensitivity was 81.4% for preterm/ giving birth subgroup and 55.9% for preterm/ not giving birth subgroup.

**Table 1.** Comparison of the mean AFP levels of the control group and the patient group with preterm labor

| Group | Number of cases | Mean AFP ng/ml | P |
|---|---|---|---|
| Control | 110 | 84.2± 45.6 | <0.001 |
| Preterm | 120 | 137.5± 59.2 | |

Data are presented as mean ± standard error

**Table 2.** The differences of groups from the cut-off values and their mean AFP levels

| Group | Number of cases | Mean AFP ng/ml | Cut-Off value ≤106.05 (%) | Cut-Off value >106.05(%) | P |
|---|---|---|---|---|---|
| Control | 110 | 84,4±45,6 | 77(70%) | 33(30%) | |
| Preterm/giving birth | 86 | 153,3±58,1 | 16(18.6%) | 70(81.4%) | <0.001 |
| Preterm/not giving birth | 34 | 97,6±40,8 | 15(44.1%) | 19(55.9%) | >0.05 |

Positive predictive value was 66.9% in preterm/giving birth subgroup, and 36.7% in preterm/not giving birth subgroup. Negative predictive value was 82.7% in preterm/giving birth subgroup, and 83.6% in preterm/not giving birth subgroup.

The mean AFP levels were significantly higher in the preterm/ giving birth patient group, when compared with the control group and preterm/ not giving birth patient group ($p<0.001$). However, there was no statistically significant difference in between the preterm/ not giving birth subgroup and the control group ($p>0.05$).

Tocolysis was performed to 86 patients in the preterm labor group. The patients were divided into two subgroups; Group A consisted of patients giving birth in the first 72 hours ( n= 57, mean AFP = 139.4±70.9 ng/ml), and Group B consisted of patients giving birth after 72 hours or who did not give birth (n= 29, mean AFP = 168.6±61.9 ng/ml). The mean AFP level was significantly higher in the group consisting of patients in whom tocolysis was performed, when compared with the control group ($p<0.001$).However, there was no significant difference in between Group A and B. The mean AFP level was higher in group B but the difference was not statistically significant. The number of patients whose AFP levels were higher than the cut-off value was 36 (63%) in Group A, and 27 (93%) in Group B. According to these findings, the percentage of patients whose AFP levels were higher than the cut-off value was significantly higher in the group consisting of patients in whom tocolysis was performed, when compared with the control group, and in Group B, when compared with Group A ($p<0.001$) (Figure 1,2).

The rate of differences of the mean AFP values of groups from the cut-off value according to the gestational weeks was compared and no statistically significant difference was found ($p>0.05$). Nevertheless, the mean AFP level according to gestational weeks was higher in the preterm/giving birth patient group, when compared with the control and preterm/not giving birth patient group ($p<0.001$) (Table 3).

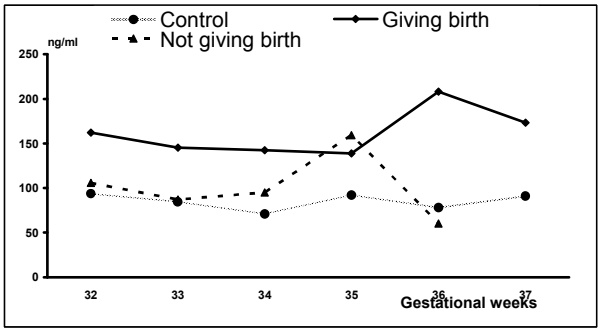


**Figure 1.** The mean AFP levels of the control group, preterm/giving birth and, preterm/not giving birth groups according to the gestational weeks.

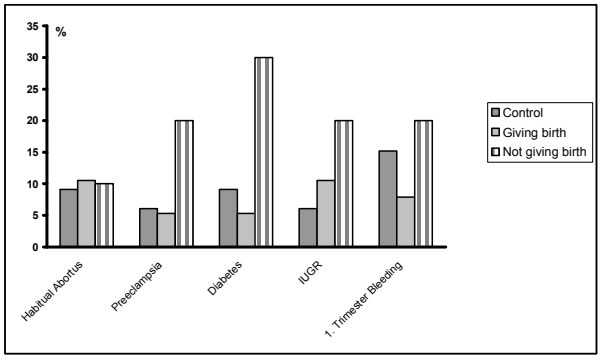


**Figure 2.** The rates of complicated pregnancies in the control group, preterm/giving birth, and preterm/not giving birth groups

**Table 3.** Comparison of the mean AFP levels of groups according to the weeks of gestation

| Weeks of gestation | Group | Number of cases | Mean AFP ng/ml | AFP mg/ml | |
|---|---|---|---|---|---|
| | | | | <106.05 | >106.05 |
| 32 | Control | 30 | 93,7±54 | 21 (70%) | 9 (30%) |
| | Preterm/giving birth | 31 | 162±67,1 | 3 (9.7%) | 28 (90%) |
| | Preterm/not giving birth | 13 | 105,6±41,4 | 4 (30,8%) | 9(62%) |
| 33 | Control | 12 | 84,4±53,7 | 8(66%) | 4(33%) |
| | Preterm/giving birth | 16 | 145,5±42,6 | 4(25%) | 12(75%) |
| | Preterm/not giving birth | 10 | 87,1±41,8 | 6(60%) | 4(40%) |
| 34 | Control | 25 | 70,8±37,7 | 19(76%) | 6(24%) |
| | Preterm/giving birth | 23 | 142,1±35,7 | 6(26%) | 17(73%) |
| | Preterm/not giving birth | 9 | 95±67,8 | 4(44%) | 15(55%) |
| 35 | Control | 15 | 92±37,1 | 9(60%) | 6(40%) |
| | Preterm/giving birth | 10 | 138,7±67,8 | 3(30%) | 7(70%) |
| | Preterm/not giving birth | 1 | 159,3 | - | 1(100%) |
| 36 | Control | 18 | 77,9±37,1 | 14(77%) | 4(22%) |
| | Preterm/giving birth | 4 | 207,1±60,1 | - | 4(100%) |
| | Preterm/not giving birth | 1 | 60,4 | 1(100%) | - |
| 37 | Control | 10 | 90,8±51 | 6(60%) | 4(40%) |
| | Preterm/giving birth | 2 | 173,1±13,5 | - | 2(100%) |
| | Preterm/not giving birth | - | - | - | - |

The mean AFP levels according to the weeks of gestation was significantly higher in the preterm/giving birth group, when compared with both the control and the preterm/not giving birth group ($p<0.001$). The relation between the rates of intrauterine growth retardation, 1st trimester bleeding, habitual abortus, preeclampsia, gestational or type 1-2 diabetes and the mean AFP levels was found to have no significance when the patient and control groups were compared (Figure 2).In the patients with a story of one or two preterm labor, there was no significant difference in between the preterm/giving birth-not giving birth groups and the control group in terms of the mean AFP values ($p>0.005$). Nevertheless, although there was no significant difference in between groups in terms of anemia incidence, the AFP level showed a statistically significant increase along with the decrease in the hemoglobin levels in the preterm/not giving birth patient group ($p<0.001$) ($r = -.061$).

## Discussion

Preterm labor is one of the most important factors affecting perinatal outcome and although too many studies are performed with the aim of establishing the predictors of preterm labor, there is no still definite predictor and no certain cut-off value established. Recent interest has been focused on MsAFP levels. Most studies have demonstrated that the elevation of the MsAFP levels in the patient group with preterm labor is statistically significant when compared with the control groups.

Davis et al suggested that the midtrimester MsAFP elevation represents increased risk in terms of preterm labor, but there is no statistically significant relation with low birth weight (4). Kua et *al* found the rate of preterm labor as 22% in patients whose elevated MsAFP levels could not be explained. The same rate was 11% in the control group. This rate increased to 47% in patients with MsAFP elevation and having sonolucent regions in their placentas (5). Simpson reported that finding shows a statistically significant association with preterm delivery, low birth weight, and preterm premature membrane rupture (6). Other studies have revealed that the association of unexplained MsAFP elevation and the increase in perinatal morbidity-mortality, low birth weight and preterm delivery, oligohydramnios, placental decollement, or intrauterine fetal exitus seems to be higher when

compared with the control group (7-9).

In our study, we did not follow-up the unexplained MsAFP levels, but rather preferred to examine the blood values of normal patients and patients with preterm labor as we thought that this would represent more objective data. As a result we found that MsAFP levels were high in preterm labor and especially in preterm delivery and our finding was in accordance with the literature. An attracting finding was that, in patient with the signs of preterm labor but who did not have preterm delivery, the MsAFP levels was not higher than the control group. Even this can suggest that MsAFP levels can predict preterm delivery. On the other hand, establishing the cut-off value is very important. This value needs to be validated with studies performed on large patient populations. Establishing MsAFP levels lower or higher than this value, diagnosing real preterm labor, establishing the progression of preterm labor and its reaction to tocolysis can lead to guiding results while selecting patients for the expectant treatment.

The reason of the association between preterm labor and MsAFP elevation could not yet be explained. However, studies up to date have highlighted that placental vascular pathologies which can deprave the uteroplacental flow, bleeding, ischemia, breaking of the fetoplacental barrier, and the fetomaternal transfusion can lead to the elevation of MsAFP levels. Hay *et al* demonstrated that the rise in the MsAFP levels depended on the spontaneous fetomaternal hemorrhage in 13 of the 150 patients referred for genetic consultation all of whom had high levels and were in between the 14-20$^{th}$ weeks of gestation (10). In a study indicating to fetomaternal hemorrhage using the Kleihauser – Betke test, the rate of fetomaternal hemorrhage was high in the group with elevated MsAFP levels (11).

In clinical application, there are no real false positive MsAFP elevations. Though not always associated with a structural malformation, an increase in the MsAFP is a marker for adverse perinatal outcome (12, 13). The principal risks are fetal death, intrauterine growth retardation, first trimester and late pregnancy bleeding and preterm delivery (8, 14).

Perkes et al examined the placental ultrasounds of patients with unexplained high MsAFP levels and found that a majority of them had cystic lesions. Postpartum evaluations revealed that these cystic spaces were regions of vascular abnormalities (15).

As a result we conclude that MsAFP elevation can be used as a predictor of preterm labor. However, this parameter needs to be evaluated in large patient populations and the cut-off value should be established. Even though the elevation of MsAFP levels of the patient group with preterm labor has the possibility to depend on fetomaternal hemorrhage, we believe that, this is another issue in need of further evaluation.

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