

## Placental alkaline phosphatase in the prediction of preterm delivery

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**Objective.** To examine the reliability of human placental alkaline phosphatase (hPLAP) in the mother's serum as a marker of premature labour among pregnant women who had no known risks for premature labour and to determine the critical value of hPLAP in pregnancies which ended up as a premature labour. **Patients and Methods.** The research was conducted in the form of a prospective study of 200 pregnant women. All the pregnant women were divided into two groups, the examinees and the control group. The value of hPLAP in serum of all pregnant women determined in the period from week 20 to 24 of gestation. > 2 median value was taken as a critical value for hPLAP. Besides descriptive statistical methods for the statistical data processing we used the  $\chi^2$  test, student t-test, Fishers test and Mann-Withneys test, logistic regression. **Results.** The number of premature labours in the examined group was 17 (11.3%), in the control group 22 (44%). The probability of premature labour is 6.1 times higher in the control group in relation to the examined group. The mean value of hPLAP in the examined group was 608.2 but in the control group 1115.6. The mean value of hPLAP in the pregnant women who gave birth prematurely was 1195 but in those who gave birth on time 632.2. There was a statistical significant difference in mean values of hPLAP. **Conclusios.** hPLAP can be used as a reliable marker of idiopathic premature labour. hPLAP values connected with the development of premature labour is 990 mU/l.

**Key words:** Preterm labour, Placental alkaline phosphatase, Prediction.

Received: 1 April 2009  
Accepted: 28 May 2009

### Introduction

According to the World Health Organisation (WHO) and the American Pediatrics Academy each delivery which occurs before

37 gestational weeks is considered a preterm delivery (1). The best and most effective prevention of preterm delivery incidence is early identification of pregnant women who belong to a group of high risk (2). Meth-

ods of identification include clinical and biochemical markers of preterm delivery. Various pieces of research have pointed out that human placental alkaline phosphatase (hPLAP) can be used as a possible marker of idiopathic preterm delivery (3).

The placental specific isozyme of Alkaline Phosphatase (PLAP) is found in the trophoblast cells of a normal human mature placenta (4). Human placental alkaline phosphatase (hPLAP) are polymorphic and heat-stabile enzymes. They are localised in the apical and basal cells of the syncytiotrophoblast plasma membrane and at the surface of cytotrophoblast chorionic villuses. Human phosphatase is a sialoglycoprotein in which glycosyl phosphoinositol is situated consisting of two identical subunits. There are high levels of this enzyme in the trophoblasts of the placenta, while it can also be traced in the lungs, endocervix and Fallopian tubes. Its creation starts at about the seventh week of gestation (5). Elevated placental alkaline phosphatase levels may signal an increased risk of preterm delivery. Placental alkaline phosphatase, a glycoprotein found in maternal serum, increases with gestational age and normally peaks at term. The odds of delivering preterm were determined greater among mothers with higher placental alkaline phosphatase levels. Elevated mid-trimester serum levels among these mothers may indicate a breakdown of the foetal membranes (6).

The aim of this study was: to examine the reliability of hPLAP in mothers serum as a marker for preterm delivery with women who do not have any of the proved risks which can cause preterm delivery, and determine the value of hPLAP which correlates with preterm birth incidence.

## Patients and Methods

The study was conducted as a prospective study and included 200 pregnant women.

Correct gestational age was determined according to the last menstrual cycle and ultrasound biometry during the first trimester. We determined gestational age at the time of delivery in pregnant women who delivered before 37 gestational weeks and the number of preterm deliveries. Pregnant women were divided into examinees and a control group. 150 pregnant women who were regularly controlled in ante-natal clinics formed the examinee group. The control group consisted of 50 pregnant women who were admitted to the Gynaecology and Obstetrics Clinic in Tuzla. They were admitted for a symptoms of preterm labour. In both groups of pregnant women none of the well known risk factors for preterm delivery incidence were present. The standards used for selection of women for the control group were: a tocolytics index less than 4, intact membranes and absence of contraindications for tocolytics therapy.

The value of hPLAP in serum was determined in all women in the period of 20 to 24 weeks gestation. In the course of pregnancy, the incidence of preterm birth was monitored. hPLAP was determined by the Elisa method using monoclonal antibodies with the help of Innotest hPLAP. Innotest is manufactured by Innogenetics, Belgium. The value  $> 2$  was taken as the critical value (a value greater than two median values). This value is expressed in mU/l.

During data processing descriptive statistical methods were used, mean values, standard deviation and the control group were compared by the  $\chi^2$  test, student t-test, Fishers test and Mann-Whitney's test. Logistic regression was used to determine whether placental alkaline phosphatase was associated with preterm birth.

## Results

The examined group consisted of 150 (100%) women, 17 (11.3%) had preterm delivery

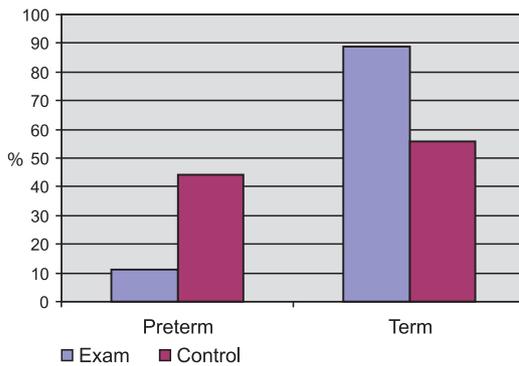


Figure 1 Number of preterm deliveries in the examined and control groups

Table 1 Gestational age at preterm delivery in examined and control groups

Weeks of gestation	Examined group		Control group	
	N	%	N	%
26-30	–	–	4	8
31-34	2	1.3	8	16
35-37	15	1.0	10	20
Total	17	11.3	22	44

$\chi^2 = 5.9$ ;  $p = 0.015$

while the number of term deliveries was 133 (88.6%). The control group consisted of 50 (100%) women, 22 (44%) had preterm delivery while the number of term deliveries was 28 (56%). The probability of preterm delivery incidence was 6.1 times greater in the control than in examined group (95% CI: 2.9-13.1),  $\chi^2 = 25.5$ ,  $p < 0.0001$ .

In the examined group there were 2 deliveries (1.3%) before 34 weeks gestation, in the control group 12 deliveries (24%) in the same period of gestation (< 34 weeks gestation). The probability of preterm delivery was 9.0 times greater in the control than in the examined group for gestational age < 34 weeks gestation (95% CI: 1.4-94.2).

The mean value of hPLAP in the control group was 1115.6 mU/l with standard deviation 377.8 and median value 460. Mean values were tested by t-test. It was shown that

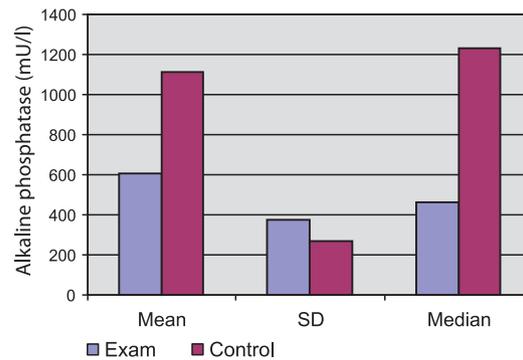


Figure 2 Value of human placental alkaline phosphatase in examined and control groups

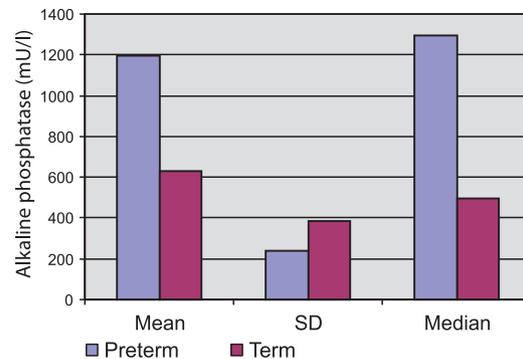


Figure 3 Value of human placental alkaline phosphatase in preterm delivery and term delivery in both groups

there was a statistically significant difference between the mean values of hPLAP in the examined and control groups ( $t = 8.7$ ;  $df = 199$ ;  $p < 0.0001$ ) (Figure 2).

Mean value of hPLAP in preterm delivery was 1195 mU/l with standard deviation 240 and median value 1295. Mean values were tested by t-test. It was shown that there was a statistically significant difference between mean values of hPLAP in preterm delivery and term delivery ( $t = 8.2$ ;  $df = 199$ ;  $p < 0.0001$ ) (Figure 3).

Following Mayer et al (7) median values calculated were used for concentration of hPLAP in preterm and term deliveries. Concentrations of hPLAP greater than two median values and their incidences in term delivery were also calculated. It was proved

by  $\chi^2$  test that there is a connection between preterm delivery incidence and hPIAP concentration ( $\chi^2 = 438$ ;  $p = 0.0001$ ) (Table 2). The Fisher exact test brought us to the same conclusion. While calculating the relation between the probability of preterm delivery and term delivery, the conclusion was reached that the probability of preterm delivery is 12.2 times greater with increased values of hPIAP. Regarding the sensitivity and specific quality of hPIAP, it was concluded that the sensitivity of the test was 71.8% and the specific quality 82.7%.

Table 2 Median value of concentration of human placental alkaline phosphatase (hPIAP) <2 (median) and >2 (median) in preterm and term delivery in both groups

Delivery	Median hPIAP < 2	Median hPIAP > 2
Preterm	11 (5.5%)	28 (14%)
Term	133 (66.5%)	28 (14%)

$\chi^2 = 43,8$ ;  $p = 0.0001$

## Discussion

Preterm delivery is the leading cause of mortality in newborns. About 65 to 70 % of foetus deaths and the incidence of early neonatal death are in children born before the end of the 37<sup>th</sup> week of gestation with body weight less than 2500 grams (8). Women with high levels of hPIAP in the midtrimester have a higher risk for preterm delivery incidence. The biological mechanisms involved in this process are unclear. Necrosis, rupture and other damage of the chorionic villuses, infarction of the placenta or ablation of the placenta can increase the levels of alkaline phosphatase of the placenta in the serum (9). This is found in women who suffer from preterm delivery and it is a clear indication of integrity disorders of the foetus membranes. Many studies have indicated the relationship between increased levels of serum thermostabile alkaline phosphatase and low

birth weight and placenta insufficiency (10). The smallest value in the control group was 730 mU/l while in the experimental group it was 150 mU/l. The highest value in the control and experimental groups was 1375 mU/l.

Thermostable hPIAP in women who have normal course of pregnancy is an indicator of placenta function and indirectly an indicator of the condition of the foetus (11). With as the pregnancy progresses, the statistical and significant growth of hPIAP in obvious. There are individual variations in hPIAP at some gestational periods in different women. It was found that the mean value of hPIAP was 1280 mU/l within the first eight weeks of pregnancy. In 28 (56%) women who suffered from preterm delivery, the value of hPIAP > 2 was found, 11 (22%) women had values < 2. The probability of preterm delivery where hPIAP value is > 2, is 12.2 times greater than term delivery. In this study a much higher percentage of pregnant women had values > 2 compared to the study by Meyers et al where 33% of women had value > 2. According to the study by that author the probability of a preterm delivery is 2.9 times greater than term delivery if the value of hPIAP is increased. High specificity means that patients who have high values of hPIAP will most likely suffer from preterm delivery. The possibility of preterm delivery increases with the increase of alkaline phosphatase level (12).

## Conclusions

According to the obtained results the following conclusions were made:

- Human placental alkaline phosphatase (hPIAP) is a reliable marker of preterm delivery with patient who do not have any proven risk of preterm delivery and the marginal value of hPIAP connected with preterm delivery is 990 mU/l.

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