CASE REPORT

Extreme elevation of placental alkaline phosphatase as a marker of preterm delivery, placental insufficiency and low birth weight

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Abstract

OBJECTIVE: Clinical case of extremely elevated levels of alkaline phosphatase (ALP) enzyme detected in the 3rd trimester of gestation, the diagnostic and therapeutic procedures, delivery and puerperium are presented. The paper also offers a review of the currently available bibliographical data of the issue.

METHODS AND RESULTS: The case presents a 23-year-old secundipara with clinical problems in her 3rd trimester, namely a generalized pruritus. The gestation had signs of asymmetrical fetal hypotrophy induced by placental insufficiency. Laboratory tests showed elevated (as much as a 10.5-fold increase) values of alkaline phosphatase enzyme, 94.05% of which was placental isoenzyme. The patient also had clinical symptoms of a preterm delivery. The spontaneous delivery occurred in 36 week of gestation. The postpuerperium values of alkaline phosphatase returned to normal.

CONCLUSION: The authors point out the potential relationship between elevated placental isoenzyme of alkaline phosphatase levels and placental insufficiency and the onset of a preterm delivery.

INTRODUCTION

Alkaline phosphatase (ALP) in blood serum is a heterogeneous mixture of organ-specific isoenzymes and enzyme variants (they have identical peptide chains but a different structure of the sacharide portion of the enzyme). Isoenzymes are synthesized mainly in the liver, bones (osteoblasts), intestine, kidneys, lungs, and placenta in pregnancy. Their role has not been fully explained (White *et al.* 1989). They are bound to the outer cell surface (Abu-Hasan *et al.* 1985; Harris 1980).

Abbreviations:

ALP	- alkaline phosphatase
CTG	- cardiotocography
G	- gestation
P	- parity
IUGR	- intrauterine growth retardation

The alkaline phosphatase isoenzymes are coded by at least four genes in humans. Three genes at the 2q34-37 chromosome code the production of placental, "placenta-like" and intestinal alkaline phosphatase isoenzyme. The fourth gene at the 1p36.1-34 chromosome codes the liver, bone and kidney alkaline phospahatse isoenzyme (Moss *et al.* 1992). Bone and liver alkaline phosphatase isoenzymes represent the major portion in a healthy adult human (Millan *et al.* 1980; Mulivor *et al.* 1985). The intestinal isoenzyme occurs only in very small concentrations (McComb *et al.* 1979, Mulivor *et al.* 1985).

The placenta plays a complex endocrine role and synthesizes specific placental enzymes during gestation (Babuna *et al.* 1996; Diczfalusy 1974). Placental isoenzyme of alkaline phosphatase is coded by a gene of the fetal genome (Maxwell *et al.* 1985). It is made by syncythiotrophoblast cells (Abu-Hasan *et al.* 1985; Harris 1980). In an uncomplicated pregnancy the alkaline phosphatase levels go up between the 1st and 2nd trimesters, specifically between gestation weeks 15 to 26 (Fishman *et al.* 1976), culminating in the 3rd trimester (Okesina *et al.* 1995). In normal conditions the placental isoenzyme accounts for 40 to 67% of alkaline phosphatase in the 3rd trimester. The alkaline phosphatase levels in pregnant women are usually two-fold the levels found in non-pregnant women. In post-puerperium the alkaline phosphatase levels return back to the physiological range (Makiya *et al.* 1992). The role of the placental alkaline phosphatase is not quite clear; it is assumed to play an important role in placental metabolism. Placental isoenzyme detected in non-pregnant women is associated with oncological diseases such as intracranial germinoma (Shinoda *et al.* 1988). When detected in pregnancy, it may be associated with HELLP syndrome, intrahepatal cholestasis, malign tumors or bone metabolism diseases (Deluc *et al.* 2007).

In the following sections the clinical case is presented of a secundipara with extremely elevated (10.5-fold) alkaline phosphatase enzyme levels diagnosed in the 3rd trimester of pregnancy. Placental isoenzyme accounted for 94.05% of the total ALP serum value. The patient exhibited clinical symptoms of placental insufficiency, IUGR (intrauterine growth retardation) and preterm delivery which had already been described (Bashri *et al.* 2007, Meyer *et al.* 1995**,** Wojcicka-Bentyn *et al.* 2004). The ALP levels returned to the physiological range after puerperium.

Tab. 1. ALP levels in gestation weeks and postpartum.

Gestation week	ALP value normal 0.54 -1.70 ukat/L
32+1	13.06
32+6	13.95
34+3	16.22
35+1	16.80
36+1	17.87
24 hours after delivery	14.09
Post-puerperium	1.19

CASE REPORT

A clinical case of a 23-year-old secundipara G (gestation) 3 P (parity) 2 is described. The patient had been treated by an allergist for atopic dermatitis since her childhood. The obstetric history included an induced delivery at term because of oligohydramnion. No other noteworthy events in her history. The patient had no problems until week 33 of the currently discussed gestation. At week 33 elevated blood pressure values, namely 151/96 mmHg were measured. Protein was found in her urine. The patient claimed she was suffering from pruritus in her upper limbs, thighs and face. The blood test showed light anemia, haemocoagulation parameters were within the physiological range and comprehensive biochemical parameters were normal with exception of the ALP which was significantly elevated at 13.06 μkat/L. The ALP levels taken in respective gestation weeks are shown in Table 1. The protein debris in urine in 24 hours was at standard levels. The abdominal ultrasound scan showed no pathological condition. Hepatoprotective therapy was applied. The obstetrical ultrasound scan showed an asymmetric hypotrophy of the fetus and oligohydramnios. The ALP levels went up to 16.22 μkat/L. Blood pressure was normal. The fetal condition was satisfactory since hypotrophy was not progressing, the flowmetric tests in the fetoplacental unit were normal and the CTG (cardiotocography) yielded normal results. In gestation week 35 the skin pruritus was getting worse despite the symptomatological treatment and the extremely elevated ALP levels were still increasing (17.87 μkat/L). The next blood tests showed normal values for the rest of the biochemical parameters. Haemocoagulation parameters were within physiological range. The blood tests showed leucocytosis, light anemia, lowered haematocrit and normal trombocyte levels. The placental isoenzyme accounted for 94.05% of the alkaline phosphatase. The CTG recorded episodes of regular contractions and the vaginal findings were progressing.

At gestation week 36 the patient had a spontaneous uncomplicated delivery. Female fetus, 2 500 g/45 cm and a 10/10/10 Apgar score was born. The 400 g placenta exhibited numerous macroscopic infarctions (Figure 1). Twenty four hours after delivery the alkaline phosphatase levels went down slightly to 14.09 μkat/L. The patient had no puerperal problems. The alkaline phosphatase enzyme level was back to a normal 1.19 μkat/L after puerperium and the patient had no clinical signs of atopic dermatitis or skin pruritus. The histopathological examination of the placenta confirmed numerous placental infarctions.

DISCUSSION

So far six cases have been described with extremely elevated alkaline phosphatase enzyme levels diagnosed in the 3rd trimester. In two cases the elevated alkaline phosphatase levels were associated with numerous placental infarctions and damaged syncytiotrophoblast (Boronkai *et al.* 2005; Vongthavarat *et al.* 2000). The third case was a pregnancy with gestational diabetes where most of the alkaline phosphatase originated in bone (Vongthavarat *et al.* 2000). In the fourth case there also was a pregnancy with gestational diabetes, with alkaline phosphatase mostly of placental origin, but in contrast to our case, the patient's ALP levels did not return back to the physiological range after delivery. In the described case, similar abnormal findings were identified in the first of kin and the ALP elevation was not associated with gestational diabetes (Wojcicka-Bentyn *et al.* 2004). In the fifth case the alkaline phosphatase was also mostly of bone origin (Safarova *et al.* 2007). The last case, published in June 2009, was a woman with an uncomplicated pregnancy who had a 17-fold increase of ALP levels in comparison with normal levels. That case was different from the third mentioned case and similar to our case since the postpuerperium ALP levels returned to the physiological range (Celik *et al.* 2009).

What causes the extreme ALP elevation in pregnancy? There is no clear answer to the question, as there is not a large enough population of patient cases described in papers. One of the possible explanations may be genetic abnormalities (Wojcicka-Bentyn *et al.* 2004). There also are discussions about a higher risk of a preterm delivery (Bashri *et al.* 2007; Meyer *et al.* 1995; Moawad *et al.* 2002; Wojcicka-Bentyn *et al.* 2004). There are authors who associate elevated ALP with the functioning of the placenta and placental insufficiency (Boronkai *et al.* 2005; Vongthavarat *et al.* 2000). Certain older publications suggested that elevated ALP may indicate delivery of a newborn with a low birth weight (Best *et al.* 1991; David *et al.* 1987).

Our presented case was in conformity with papers finding that ALP is elevated at placental insufficiency, a spontaneous delivery at 36 week of pregnancy confirm case of preterm delivery, and with papers confirming elevated ALP at delivery of infants with low birth weights.

CONCLUSION

Extreme elevation of alkaline phosphatase in the 3rd trimester of gestation may be an important marker of imminent placental insufficiency, preterm delivery and can also be a marker of a newborn with a low birth weight.

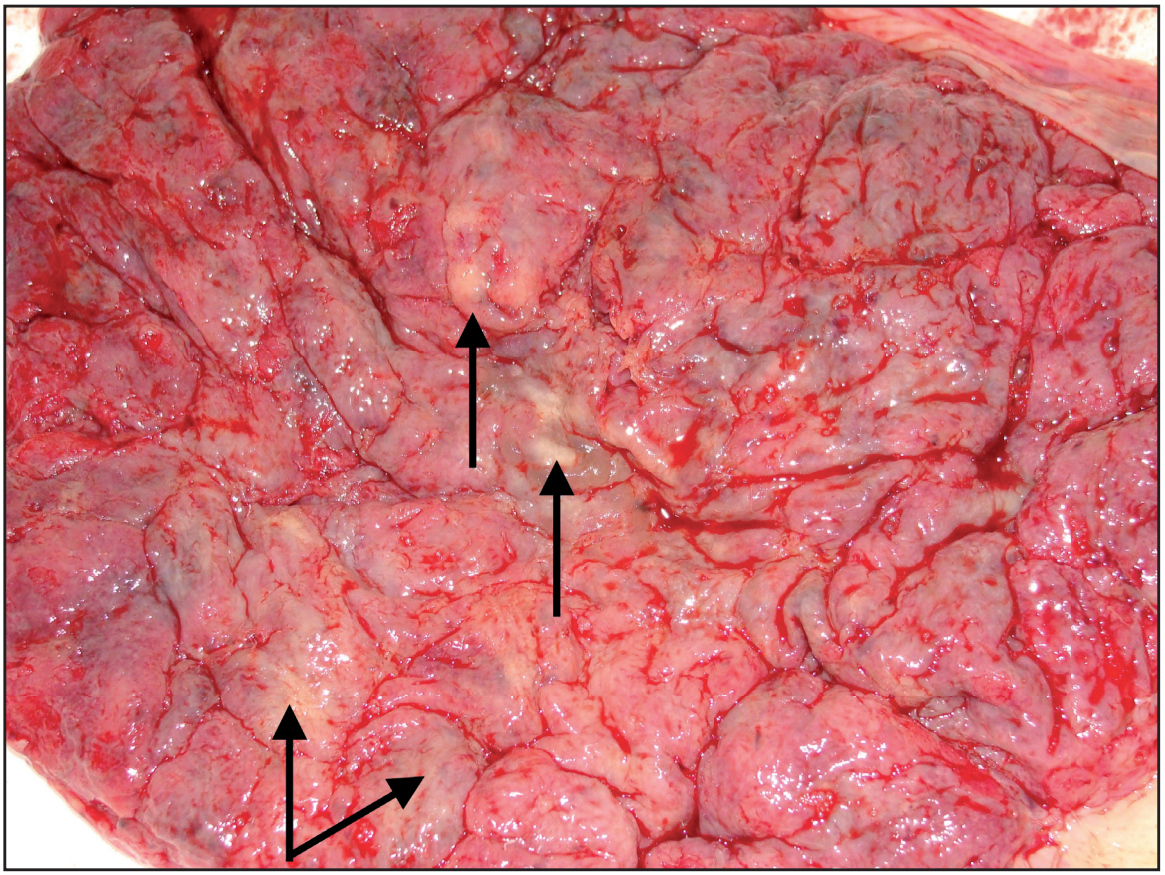

Fig. 1. Placenta with numerous infarctions marked with arrows (detail).

REFERENCES

1 Abu-Hasan NS, Sutcliffe RG (1985) Placental alkaline phosphatase integrates via its carboxy – terminus into the microvillous membrane: its allotypes differ in conformation. Placenta. **6**: 391–404.
2 Babuna C, Yemen E (1996) Enzymatis determination of placental function. Am J Obstet Gynecol. **95**: 925–934.
3 Bashri A, Maor E, Shneider E (2007) Positive placental staining or alkaline phosphatase corresponding with extreme elevation of serum alkaline phosphatase during pregnancy. Arch Gynecol Obstet. **275**: 211–214.
4 Best RG, Meyer RE, Shipley CF (1991) Maternal serum placental ALP as marker for low birth weight. Result of a pilot study. South Med J. **84**: 740–742.
5 Boronkai A, Than NG, Magenheim R (2005) Extremely high maternal alkaline phosphatase serum concentration with syncytiotrophoblastic origin. J Clin Pathol. **58**: 72–76.
6 Celik H, Tosum M, Cetinkaya MB, Bektab A (2009) Markedly elevated serum alkaline phosphatase level in an uncomplicated pregnancy. J Matern Fetal Neonat Med. **22**: 705–707.
7 David J, Broc H, Barron L (1988) Measurement of placental ALP in maternal plasma as an indicator of subsequent low birthweight outcom. Br J Obstet Gynecol. **95**: 79–83.
8 Deluc C, Costedoat-Chalumeau N, Saadoun D (2007) Elevation of ALP in pregnant patient with antiphospholipid syndrom, HELLP syndrom or not? Rheumathology. **27**: 1–2.
9 Diczfalusy E (1974) Endocrine functions of the human fetus and placenta. Am J Obstet Gynecol. **199**: 419–429.
10 Fishman WH, Ghos NK (1967) Osoemzymes of huma alkaline phosphatase. Adv Clin Chem. **10**: 255–270.
11 Harris H (1980) The principles of human biochemical genetics. Ed 3 Elsevier/North Holland. Amsterdam.
12 Makiya RL, Thornell LE, Stigbrant T (1992) Placental alkaline phosphatase a GPI anchored protein, is clustered in clathrin – coated vesicels. Biochem Biophys Res Commun. **183**: 803–808.
13 Maxwell, DJ, Blauk, K, Johnson, RD (1985) Activities of alkaline in first trimester chorion biopsy tissue. Prenat Diagn. **5**: 283–286.
14 Meyer ER, Thompson SJ, Addy ChL, Garrison ZC, Best RG (1995) Maternal serum placental alkaline phosphatase level and risk for preterm delivery. Am J Obstet Gynecol. **173**: 181–186.
15 Millan JL, Whyte MP, Avioli LV (1980) Hypophosphatasia (adult form): quantitation of serum alkaline phosphatase isoenzyme activity in a large kindred. Clin Chem. **26**: 840–845.
16 Moawad AH, Goldenberg RL, Mercer B, Meis PJ, Iams JD, Das A (2002) The preterm prediction study: The value of serum alkaline phosphatase, alfa fetoprotein, plasma corticotropin – releasing hormone and other serummarkers for the prediction of spontaneous preterm birth. Am J Obstet Gynecol. **186**: 990–996.
17 Moss DW (1992) Perspectives in alkaline phosphatase research. Clin Chem. **38**: 2486–2492.
18 Mulivor RA, Bocelli D, Harris H (1985) Quantitative analysis of alkaline phosphatases in serum and amniotic fluid: comparison of biochemical and immunologic assays. J Lab Clin Med. **105**: 342–348.
19 Okesina AB, Donaldson D, Lascelles PT (1995) Effect of gestation age on levels of serum ALP isoenzymes in healthly pregnant women. Int J Gynecol Obstet. **48**: 25–29.
20 Safarova A, Ozgur B, Dogan E (2007) Origin and significance of extremely elevated serum alkaline phosphatase activity during normal pregnancy. Tur Klin J Obstet Gynecol. **17**: 405–408.
21 Shinoda J, Yamada H, Sakai (1988) Placental alkaline phosphatase as a tumor marker for primar intracranial germinom. J Neur. **68**: 710–720.
22 Vongthavarat V, Nurnberg M, Balodimos N (2000) Isolated elevation of serum alkaline phosphatase level in uncomplicated pregnanncy: A case report. Am J Obstet Gynecol. **183**: 505–506.
23 White MP (1989) Alkaline phosphatase: physiologic role explored in hypophosphatasia. In: Peck WA., editor. Bone and Mineral Research. Vol. 6. Elsevier Science Publishers, B. V. (Biomedical Division). Amsterdam. p. 175–218.
24 Wojcicka-Bentyn J, Czajkowski K, Sienko J (2004) Extremely elevated activity of serum alkaline phosphatase in gestational diabetes: A case report. Am J Obstet Gynecol. **190**: 566–567.