Origin and Significance of Extremely Elevated Serum Alkaline Phosphatase Activity During Normal Pregnancy

NORMAL GEBELİKTE AŞIRI YÜKSELMİŞ SERUM ALKALEN FOSFATAZ AKTİVİTESİNİN KAYNAĞI VE ÖNEMİ

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Abstract

Human blood serum contains ALP isozymes of hepatic, osteal, renal and intestinal origin. In pregnancy a heat stable placental isozyme of ALP appears in blood plasma, reaching the highest values in the third trimester. The effect of pregnancy upon the maternal skeleton is not fully understood. The increase in ALP levels during pregnancy may be due to elevation of bone specific ALP.

A case of 29 year old pregnant women admitted to our clinic with thrombocytopenia and extremely elevated (> 10 folds) serum ALP levels. Abdominal ultrasonographic scan revealed no hepatobiliary disease or there was no apparent bone disease. Alkaline phosphatase isozyme electrophoresis was applied to determine the origin of ALP. It mostly belonged to bone tissue (85.8%). Serum total ALP level at 36 weeks of gestation was 1066 U/l. Before delivery at 38 weeks of gestation ALP level was 1369 U/l. After delivery, the ALP activity decreased but did not return to normal range.

The very high serum levels of ALP in third trimester of pregnancy does not always due to placental isoenzyme. Some individuals may have an exaggerated physiological response in pregnancy resulting in extremely elevation of serum markers of bone formation

Key Words: Alkaline phosphatase; pregnancy, isoenzymes; bone

Özet

Serumda karaciğer, kemik, böbrek ve bağırsak kaynaklı ALP izoenzimleri bulunmaktadır. Gebelikte ise serumda ısıya dayanıklı plasenta kaynaklı ALP izoenzimi ortaya çıkmaktadır ve enzim seviyeleri 3. trimesterda en yüksek düzeye ulaşmaktadır. Gebeliğin anne iskelet sistemi üzerine olan etkileri tam olarak anlaşılamamıştır. Gebelikte artan ALP seviyeleri kemik kaynaklı olabilir.

29 yaşında gebe trombosit düşüklüğü ve on kattan daha fazla olan aşırı derecede artmış ALP seviyelerinin tespit edilmesi üzerine kliniğimize başvurdu. Abdominal ultrason incelemesinde karaciğer ve safra sistemine ait bir bulgu tespit edilmedi. Hastada bariz bir kemik hastalığı da yoktu. ALP izoenzim elektroforezi yapılarak, ALP seviyesindeki artışın %85 kemik kaynaklı olduğu tespit edildi. Serum ALP seviyesi 36. gebelik haftasında 1066 U/l olarak tespit edildi. Doğumun gerçekleştiği 38. haftada ALP seviyesi 1369U/l olarak ölçüldü. Doğum sonrası ALP seviyesi düştü ancak normal sınırlara gerilemedi.

Gebeliğin 3.trimesterında görübilecek aşırı yüksek ALP seviyeleri her zaman plasenta kaynaklı olmayabilir. Bazı bireyler gebeliğin hormonal değişikliklerine aşırı duyarlı olabilir ve bu kişilerde kemik yapım belirteçleri aşırı yüksek değerlere ulaşabilir.

Anahtar Kelimeler: Alkalen fosfataz; gebelik; izoenzim; kemik

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Human blood serum contains ALP isozymes of hepatic, osteal, renal and intestinal origin. In pregnancy a heat stable placental isozyme of ALP appears in blood plasma, and its activity increases progressively, reaching the highest values in the third trimester. This usually results in doubling in the total alkaline phosphatase (ALPt) level compared with nonpregnant women of the same age. Total ALP activity returns to normal levels within 20-24 weeks after delivery. Elevated ALPt activity may be due to osteoporosis or increased bone turnover as occurs in malignancy or metabolic bone disorders such as osteomalacia, usage of hepatotoxic medications and biliary pathology.

Since increase in ALPt is an expected situation during normal gestation, elevations due to a disease condition may be masked during pregnancy.

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Here, we report a case in which a patient with extremely elevated ALPt level resulting from the increase of its osteal isozyme was detected in the third trimester of pregnancy and subsequently did not resolve in puerperium. We also reviewed the differential diagnosis of this phenomenon.

Case Report

A 29 years old woman, gravida 1 admitted to our clinic at 36 weeks of gestation for the investigation of thrombocytopenia with a platelet counts less than $100X10^9$/l and increased total ALP level (1066 U/l). The patient's medical history revealed past hepatitis A virus infection but there was no renal, bone or other systemic diseases and hepatotoxic or nephrotoxic medication use was not noted. Blood studies undertaken at time of admission revealed normal biochemical and hematological parameters including total protein, albumin, urea, uric acid, creatinine, total bilirubin, alanine aminotransferase, aspartate aminotranferase, gamma glutamyl transferase, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, lactic acid and electrolytes (Na, K, Cl), coagulation system (activated partial thromboplastin time, international normalized ratio, protrombin time), white and red blood cell counts, hemoglobin concentration and hematocrit level. Thyroid function tests including (free T4, free T3, and thyroid stimulating hormone) were all within normal limits. Alkaline phosphatase isozyme electrophoresis was applied to determine the origin of ALP. It mostly belonged to bone tissue (85.8%). The serum ALPt activity was 1369 U/l at 38 weeks of gestation and platelet count was $134x\ 10^9$/L. The woman delivered vaginally a healthy male infant (2727 g/47 cm) at 38 weeks gestation. Complete blood count test made during first 24 hours after delivery showed low platelet count ($74\ x\ 10^9$/L), low hemoglobin (9.9 g/dl), and low hematocrit (28.6%), normal white blood cell count 9.3/L. Abdominal ultrasonographic scan revealed no gynecologic, renal, hepatic, and biliary tract abnormalities. Platelet count returned to normal range within 4 days. The biochemical parameters other than ALPt (948 U/L) remained within normal limits. The serum osteocalcin level was high 21.2 ng/ml (reference range 3.1-13.3 ng/ml). The parathyroid hormone level was normal 41.1 pg/ml (reference range 12-72 pg/ml). The 25-hydroxy-vitamin D_3 was normal 25 µg/ml (reference range 7.6-75 ng/ml). The urinary calcium was low 12.75 mg/24 hours (reference range 100-320 mg/24 hours). The urinary creatinine was normal 0.82 g/24 hours (reference range 0.6-1.6 g/24 hours). Thyroid function tests, antithyrogobulin antibody and antithyroid antibody levels were all in normal range on the 4^{th} day after delivery. Blood studies undertaken on the 5^{th} postpartum week revealed that ALPt activity was 338 U/l, serum osteocalcin level 51.6 ng/ml. Serum 25-hydroxy-vitamin D3 was normal 16 ng/ml. Urinary deoxypyridinoline was normal 3.4 nM/mMcre (reference range 3-7.4 nM/mMcre), urinary calcium was low 26.4 mg/24 hours and erythrocyte sedimentation rate was 15mm/hr (reference range is 0-20 mm/hour for this age group). The ALPt level was 470 U/l at the postpartum 6^{th} month.

Discussion

The effect of pregnancy on bone metabolism has been studied by several groups and an increase in bone turnover occurring in late pregnancy has been postulated.[1-3] Bone biopsies from early (12-14 weeks) and late pregnancies (38-40 weeks) suggested that there may be a two-phase bone response to pregnancy with early phase of bone resorption and later bone formation phase.[4]

Recent developments on biochemical markers for bone turnover have increased the methods available to study bone metabolism.[5] In general, bone formation markers tend to be measured in serum samples whereas bone resorption markers are measured in urine.[6] Bone formation can be assessed by bone-specific alkaline phosphatase, which is produced by osteoblasts and reflects osteoblastic activity. Osteocalcin is an other marker of bone formation and it is not detected (less than 0.2 micrograms/L) after the first trimester in the majority of pregnant women but reappears within 48 hours after delivery that suggest placental clearance of this peptide.[7] Therefore using osteocalcin

as a marker of bone turnover during pregnancy may give rise to incorrect results. Bone resorption markers pyridinoline, deoxypyridinoline, and N-telopeptide are all breakdown products of type 1 collagen.[8,9] Deoxypyridinoline is thought to be specific for bone collagen breakdown.[9]

Studies of bone turnover markers suggest substantial biologic activity of bone during pregnancy. In publications, bone specific ALP was found to be either low in both first and third trimesters,[3] or elevated to normal or higher levels.[1,7,10] In a prospective study in 20 women, serum bone specific ALP and osteocalcin levels have been measured during their first full term pregnancies until 12 months postpartum. In the study all bone turnover markers increase during pregnancy and fail to reach baseline levels even after 12 months postpartum. The bone specific ALP levels change in a range of 15-26.2 U/l during the third trimester. The authors have suggested that the calcium needed for infant growth during pregnancy and lactation may be supplied at least in part by the maternal skeleton.[10] In an other study, it has been shown that bone formation markers show a biphasic pattern with decreases from baseline to the first (total ALP, bone specific ALP) or second (Osteocalcin) trimester, respectively, and a significant increase is seen in the third trimester and postpartum.[11] In a longitudinal study Rodin et al[7] have shown that bone specific ALP isozyme is elevated during the third trimester compared with early pregnancy and this elevation was still apparent at the end of the puerperium suggesting increased bone turnover.

To our knowledge, only 4 previous cases, with markedly increased serum ALP levels in the last trimester of pregnancy, have been reported in the English literature. In the first 2 cases, ALP elevations have been related to placental infarction and microscopic damage to the villous syncytiotrophoblast.[12,13] In the third report there was a case with gestational diabetes who had an isolated peripartum elevation of ALP mostly originating from bone tissue.[14] In our case ALP is from osteal origin too. Similarly in the fourth case a pregnancy complicated with gestational diabetes but ALP elevation was of placental origin, and like third case no relationships between the gestational diabetes mellitus and elevated ALP have been detected.[15]

In our case the previous test results about biochemical, hematological and bone turnover parameters during first and second trimesters are not known. However the results during the third trimester and postpartum period showed that; the bone formation markers osteocalcin and ALP isozyme of osteal origin increased much more than expected in normal pregnancy. The bone resorption markers were normal. The ALP which is originated from neutrophil is encoded by the same genetic locus for bone specific ALP, therefore ELISA may give rise to false positive test result for the levels of ALP because of this structural homology.[16] However in our case an acute inflammatory event which may give rise to neutrophilia induced increase of ALP was not detected. This marked elevation of ALP may also be caused by the hormonal status of pregnancy. The mechanisms controlling the skeletal changes during the course of pregnancy are still unknown. Alternatively, it is possible that some individuals may have an exaggerated physiological response in pregnancy resulting in a large alteration in their bone mineral density. It is thus possible that some individuals have more marked bone resorption in the first and second trimesters than normally anticipated and perhaps the increased bone formation in the third trimester and postpartum period may be due to compensate the unexpected bone loss in genetically determined susceptible patients.

In conclusion, elevations in total ALP during pregnancy, labor and post partum periods cannot be assumed to arise only from placenta, and therefore markedly elevated levels should further be investigated to determine the specific isoenzyme. However even extremely elevated levels of ALP originating from bone tissue does not always mean pathologic.

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