The significance of a high alkaline phosphatase (ALP) in pregnancy

Leeds Pathology

The Leeds Teaching Hospitals NHS
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Background

A 30 year old female with a prima gravida singleton pregnancy presented with hypertension during the 3rd trimester of pregnancy following a non-complicated 1st and 2nd trimester. After admission, she was found to have a significantly raised protein creatinine ratio of >110 mg/mmol, ascribed to a variant form of pre-eclampsia and a very elevated ALP of 1857 iU/L (non-pregnant adult reference range 30-130 iU/L) (Figure 1).

Differential diagnosis of an extreme elevation in ALP in pregnancy may include haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, intrahepatic cholestasis, other liver or bone diseases which must be excluded. During normal pregnancy, the placenta produces an ALP isoform, and can reach four times the non-pregnant adult reference range in the 3rd trimester (1). Several case reports in the literature have shown that an exaggerated increase in ALP during pregnancy in the absence of any specific disorder may indicate placental injury which can lead to intrauterine growth restriction (IUGR) and may be a marker for low birth weight and pre-term delivery (2).

Further investigations

In this patient liver function markers (including coagulation assessment and bile acids) were normal. Furthermore, an ultrasound scan of the liver showed no abnormalities excluding liver pathology as a cause. Bone disease was thought to be unlikely as she had a normal calcium with no significant increase in PTH. ALP isoenzyme analysis was requested as the source of the significantly elevated ALP remained unclear. This showed a marked increase in the placental isoform of ALP (Figure 2). Numerous 3rd trimester ultrasound scans found the foetus small for gestational age with oligohydramnios, raised umbilical resistance and placental insufficiency which is an uncommon but serious complication of pregnancy.

Patient outcome

At 33 weeks gestation, the patient had an emergency Caesarean section and delivered a newborn with IUGR and a very low birth weight (< 1.3 kg). Post-partum, her ALP decreased within 5 days to <1000 iU/L and she was prescribed labetalol to treat her high blood pressure. Histopathological examination of the placenta showed an accelerated villous maturation for gestational age with features in keeping with pre-eclampsia and a massive histiocytic intervillositis, which has been previously associated with a raised placental ALP.

Biochemistry

ALP concentrations with stage of pregnancy

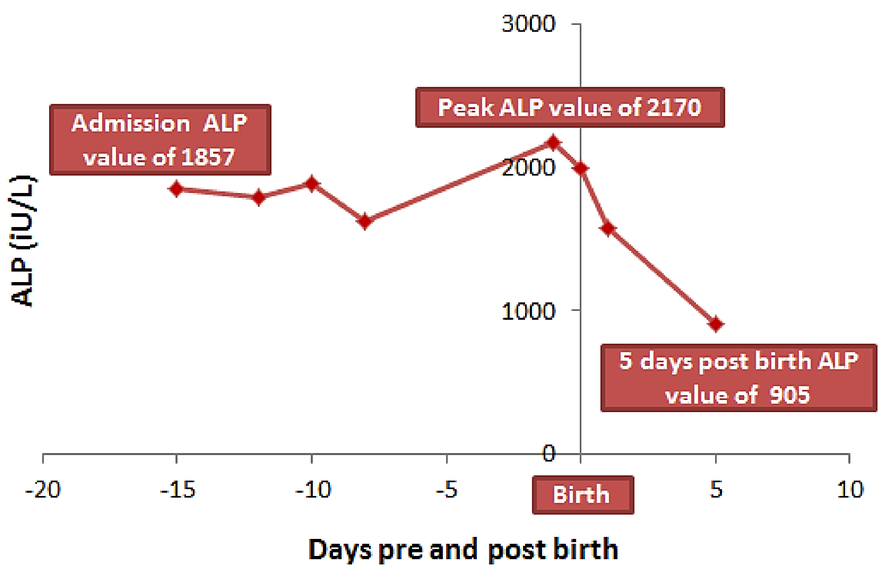

Figure 1: ALP concentrations with stage of pregnancy. Biochemistry showed persistent extreme elevation of alkaline phosphatase (ALP), with a peak value of 2170 iU/L at 32+6 weeks gestation (non-pregnant adult reference range 30-130 iU/L). Post-natally a decline in ALP concentration was observed.

ALP isoenzyme analysis (York)

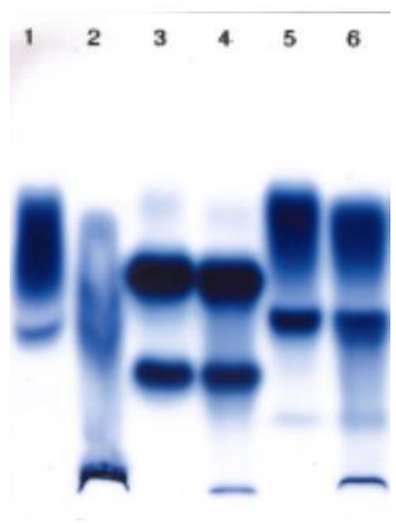

Figure 2: ALP isoenzyme analysis. The patient's sample is shown in lane 3 (no lectin) and lane 4 (with lectin) demonstrating a classical placental ALP with two characteristic bands. Lanes 1 and 2 show a typical bone isoform pattern and lanes 5 and 6 show a typical liver (and biliary) isoform pattern.

Discussion

The aetiology of a massive histiocytic intervillositis was unknown in this patient but felt to represent an immune mediated reaction and is frequently associated with early pregnancy loss, IUGR, and stillbirth. Previous case reports have quoted an association with a raised placental ALP likely reflecting placental damage and increased production of ALP by the brush border membranes of the syncytiotrophoblasts (3).

Extreme elevations of ALP in pregnancy require further investigation as they can indicate significant placental damage which may have an impact upon the pregnancy and foetal development. ALP isoenzyme analysis can have a role in pregnancy in differentiating the different possible sources of an elevated ALP.

(1) Guarino et al. The interpretation of liver function tests in pregnancy. Best Practice & Research Clinical Gastroenterology, 2020, vol. 44-45
(2) McErlean & King Does an abnormally elevated maternal alkaline phosphatase pose problems for the fetus? BMJ Case Report, 2019, vol. 12
(3) Marchaudon et al. Chronic histiocytic intervillositis of unknown etiology: Clinical features in a consecutive series of 69 cases. Placenta, 2011, vol. 2