CASE REPORT

Does an abnormally elevated maternal alkaline phosphatase pose problems for the fetus?

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SUMMARY

We report a potential association between an abnormally raised pregnancy level of alkaline phosphatase (ALP) and intrauterine growth restriction (IUGR). There are few reports of women with abnormally high ALP during pregnancy. However, there is work to suggest an association with placental insufficiency, low birth weight and preterm delivery. In conjunction with a rising ALP, fetal IUGR and intermittent absence of umbilical artery end diastolic flow had evolved. A greatly elevated ALP may be a marker for placental insufficiency and IUGR.

BACKGROUND

The enzyme, alkaline phosphatase (ALP), is derived mostly from liver and bone but is also found in the intestine, kidney and placenta.[1] An increase in ALP production occurs when tissues are functionally disturbed, for example, hepatic obstruction or greatly stimulated, for example, the placenta in pregnancy. During pregnancy, levels may reach three times the upper limit of normal (30–130 IU/L).[2] We present a case of a 31-year-old woman who had a significantly elevated ALP of 1259 IU/L at 26 weeks gestation. At 33 weeks gestation, she underwent caesarean section because of evolving intra uterine growth restriction (IUGR) and abnormal Doppler studies. This case report was prepared following the CAse REport guidelines and written informed consent was obtained from the patient.[3]

CASE PRESENTATION

This 31-year-old female is gravid 2 para 1 with an uncomplicated first pregnancy. She had documented normal liver function tests preconception and a background of iron deficiency anaemia. She had an uncomplicated antenatal course until she self-referred at 26+5 weeks gestation with a headache. She had a 1-day history of frontal headache, which eased with paracetamol. Clinical examination findings were normal, as were laboratory indices apart from a markedly raised ALP: 1259 IU/L (normal range for pregnancy: 32–418 IU/L).[2] Liver ultrasound and full bone profile were reported as normal.

ALP isoenzymes showed a normal pattern and so we hypothesised that the additional level of enzyme was of placental origin.

The ALP level continued to rise (figure 1). Serial fetal growth had been measuring along the 40–50th centile but at 33+3 weeks, it was noted that fetal growth had dropped to the fifth centile, together with a high resistance index on umbilical artery Doppler ultrasound and demonstrable intermittent absent end diastolic flow. Caesarean section was performed and a live female infant weighing 1515 g delivered. The liquor was clear at delivery. Her first baby had weighed 3275 g and she had no additional risk factors for IUGR in the index pregnancy.

The placenta weighed 372 g and histology showed villous maturity in keeping with third trimester gestation. There was no villitis, funisitis, acute chorioamnionitis, associated infarction, thrombosis, haemosiderin deposition, meconium staining or other abnormality. There was a small chorioangioma thought unlikely to be of clinical significance.

The ALP level had returned to normal 7 weeks post partum.

OUTCOME AND FOLLOW-UP

The female infant in this case is doing well at 1 year of age and has met all developmental milestones.

DISCUSSION

Despite the fact that there have been few reported cases of markedly raised ALP during pregnancy, it has been suggested that it could be a marker for placental insufficiency,[4–8] low birth weight[9 10] and preterm delivery.[4]

It is almost three decades since the publication of Brock,[9] Best[10] and Meyer's[4] work on maternal serum ALP and its association with placental-mediated fetal problems. Little has appeared in the interim apart from sporadic and isolated case reports.[6–8 11]

Cellular enzymes and proteins are typically released from damaged muscle tissue and organs. Circulating levels of these proteins and enzymes are measured and used to aid diagnosis, for example, myocardial infarction.[4 5 7] Similarly, elevated circulating ALP may be a marker of placental injury.[4 5 7] Cases of elevated ALP in pregnancy have demonstrated placental infarction[7 8] and microscopic damage to the villous syncytiotrophoblast.[6] A high or acutely rising ALP could be a useful tool to identify high-risk pregnancies and underlying placental damage.[7]

The placenta plays a crucial role in fetal development and IUGR can be considered a placentation disorder.[12] Recent evidence suggests that microRNAs (miRNAs), which regulate gene

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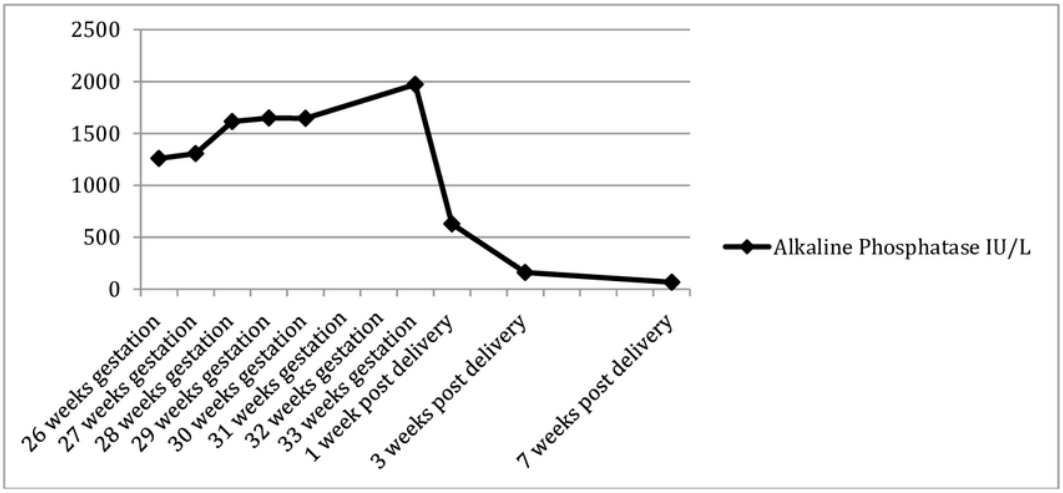

Figure 1 Rising alkaline phosphatase (IU/L) versus time.

expression and are mostly expressed in the placenta, have a key role in the pathogenesis of IUGR.[12 13] Higher levels of circulating extracellular miRNA has been associated with pregnancies which progress normally.[13 14] Other studies have shown a varied expression of miRNAs in IUGR.[12] Epigenetics may be the reason for selective miRNA expression and account for these variations.[12] Future research may be able to identify a panel of maternal biomarkers that will enable early detection of IUGR.[12]

Our patient was fortuitous in presenting with an unrelated issue (headache) and in undergoing baseline laboratory screening investigations. The isolated finding of a markedly raised ALP provoked closer monitoring, which allowed for early detection of fetal growth restriction and intervention.

This case report supports the previously noted association of an abnormally raised ALP and IUGR. However, a limitation of this case report is that this association may not be applicable in patients in general.[3]

In conclusion, we believe that an abnormally elevated and rising ALP may be a potential marker for placental dysfunction and that indeed it may pose a problem for the fetus.

Learning points

- During pregnancy, alkaline phosphatase may reach three times the upper normal limit.
- An abnormally elevated or rising alkaline phosphatase may be a marker of placental dysfunction.
- In cases with an abnormally elevated alkaline phosphatase more frequent monitoring may be indicated.

Contributors SM was directly involved in the care of this patient, obtained informed consent and wrote up the main body of the case report. CK was the supervising consultant who made key clinical decisions and edited the manuscript.

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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect