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Isolated markedly elevated maternal alkaline phosphatase in the third trimester: a potential marker of placental dysfunction and low birth weight

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INTRODUCTION

Alkaline phosphatase (ALP) increases physiologically during pregnancy, mainly in the third trimester, due to placental and bone contributions [1]. While this elevation is typically benign, extreme or rising levels may signal pathological conditions. Existing literature offers mixed evidence on the association between ALP and adverse birth outcomes (ABO), such as small-for-gestational-age (SGA) infants, preterm birth (PTB), or placental insufficiency [2-4]. This case report aims to contribute to this

ABSTRACT

Background. Alkaline phosphatase (ALP) levels physiologically increase in pregnancy, primarily due to placental production. However, abnormally elevated ALP levels may be correlated with placental dysfunction and adverse birth outcomes.

Case presentation. We report the case of a 36-year-old nulliparous woman with no significant medical history, who presented with isolated elevated ALP levels from 30 weeks of gestation, reaching a peak of 3,173 U/L at 37 weeks. Other hepatic parameters and bile acids remained within normal ranges throughout pregnancy. Serial foetal growth assessments revealed a progressive reduction of percentile, with estimated foetal weight at the 12th percentile near term. Labor was induced at 39 weeks and 2 days due to foetal growth restriction. A female neonate weighing 2,680 g (approximately 10th percentile) was delivered vaginally. Histopathological analysis of the placenta revealed third-trimester villous maturity with signs of hypoxic-ischemic damage and extensive intervillous fibrin deposits.

Conclusions. This case supports the hypothesis that isolated markedly elevated ALP levels in late pregnancy may be a marker of subclinical placental dysfunction and foetal growth restriction. In the absence of cholestasis or hepatic pathology, elevated ALP should prompt close foetal monitoring and placental evaluation.

limited body of evidence by presenting a case of isolated and markedly elevated maternal ALP levels in late pregnancy, and to explore its potential association with placental histopathological abnormalities and reduced birth weight.

CASE PRESENTATION

A 36-year-old gravida 1, para 0 woman without comorbidities was followed during her pregnancy. Her routine labs were unremarkable until 30

weeks, when ALP rose to 380 U/L. This elevation progressed despite normal liver function and bile acid levels, peaking at 3173 U/L at 37 weeks. No cholestasis or bone pathology was found. Serial ultrasound assessments showed amniotic fluid at the lower end of normal and decreasing foetal growth percentiles (down to the 12th percentile). The patient was admitted for induction at 39 weeks and 2 days. Labor was initiated with dinoprostone and complicated by uterine tachysystole, managed with atosiban. She delivered a 2,680 g female baby with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The placenta, weighing 353 g, showed signs of chronic hypoxic-ischemic injury with fibrin deposition.

DISCUSSION

This case adds to the developing evidence suggesting that isolated ALP elevation in late pregnancy may reveal subclinical placental pathology. Alkaline phosphatase is a hydrolase enzyme present in multiple tissues, including liver, bone, bowel, kidney, and placenta. During pregnancy, the predominant form circulating in maternal serum is the placental isoenzyme, synthesized by the syncytiotrophoblast [1, 3]. Although physiologic increases in ALP are expected as gestation progresses, reaching two to three times the upper limit of normal, marked or disproportionately rising levels, in the absence of hepatic or skeletal pathology, may signal abnormal placental function or integrity [5, 6].

While the large cohort study by Zhang *et al.* paradoxically associated higher ALP levels with opposite perinatal outcomes, including higher birth weight and reduced risks of preterm birth and SGA, other data, according to our findings, suggest that extremely elevated ALP may indicate incipient placental insufficiency [2]. McErlean *et al.* described a similar case of significantly raised ALP in the third trimester associated with intrauterine growth restriction (IUGR) and Fetal Doppler abnormalities suggestive of uteroplacental insufficiency [7].

In addition to these reports, more recent literature provides further insight into the heterogeneous implications of markedly elevated ALP levels in pregnancy. Stanley *et al.* described a case with a 30-fold increase of placental ALP, yet with an uncomplicated term delivery and no evidence of placental pathology, underscoring that extreme elevations do not invariably predict adverse outcomes [6]. Conversely, Wilkof-Segev *et al.*, in the largest available

case series (21 pregnancies), reported that ALP levels exceeding 1,000 U/L were frequently associated with complications such as gestational diabetes, hypertensive disorders, preterm birth, and, in some cases, placental vasculopathy or inflammation [3]. Similar associations between excessive placental ALP secretion and hypoxic-ischemic placental injury had also been noted in earlier observational studies [8,9].

Placental ALP originates predominantly from syncytiotrophoblast membranes, where it plays a role in nutrient transport and placental barrier function. Its levels increase progressively throughout gestation, reflecting placental growth and villous maturation. However, excessive or disproportionate elevations may reflect pathological processes. In particular, intervillous fibrin deposition, as identified in our case, is consistent with chronic hypoxic-ischemic injury and may disrupt the syncytiotrophoblastic surface, leading to increased ALP release into the maternal circulation. This mechanistic link supports the hypothesis that markedly elevated ALP can serve as a biochemical marker of occult placental dysfunction.

This apparent contradiction may be explained by the heterogeneity of ALP isoenzymes and their differential expression in response to physiologic *versus* pathologic inducements. Indeed, while some elevations may result from enhanced syncytiotrophoblastic activity during normal placental maturation, others may reflect cellular stress or injury, leading to ALP outflow into maternal circulation. The divergence in clinical outcomes likely reflects differences in isoenzyme predominance, maternal comorbidities, and placental resilience.

In our case, the extreme elevation of ALP was not complemented by liver enzyme abnormalities, cholestasis, or bone disease, supporting a placental origin. The histological examination of the placenta confirmed third-trimester villous maturity but also revealed extensive intervillous fibrin deposition, consistent with chronic hypoxic-ischemic injury. This aligns with other reports that identified histological evidence of vascular malperfusion or fibrin deposition in association with disproportionate ALP elevations [3, 5]. These findings underscore the potential role of ALP as a non-invasive biochemical marker of occult placental dysfunction, even in the absence of explicit clinical signs such as pre-eclampsia or cholestasis.

Altogether, these observations support the notion that isolated and disproportionate ALP elevation in

late pregnancy should not be dismissed as benign but rather considered as a potential early marker of placental maladaptation. Future investigations should also explore standardized thresholds for clinical alarms and assess whether serial ALP monitoring could serve as an adjunct tool in the early detection of placental insufficiency.

CONCLUSIONS

Severe isolated ALP elevation in the absence of other liver abnormalities may be an early sign of placental dysfunction. In such cases, enhanced surveillance, including Doppler studies and growth monitoring, should be considered. Further research is warranted to define ALP thresholds and isoenzyme profiles associated with adverse outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

M.G.S.: Conceptualization, project administration, supervision. O.D.: Methodology, data collection, investigation, data curation; visualization, writing – original draft; writing – review & editing. O.D., M.G.S.: Writing – review & editing.

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The authors declare that they have no conflict of interests. O.D. is a board member.

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Informed consent

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Data sharing

N/A.

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