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Ceruloplasmin and Alkaline Phosphatase Levels in Preterm Delivery

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Preterm birth (PTB) is a major determinant of neonatal mortality and morbidity. Preterm babies are prone to serious illness or death during the neonatal period. PTB is one of the unresolved problems in clinical obstetrics and one of the greatest threats to the developing fetus, there is need to determine predictive biomarker for preterm delivery. Therefore present study aimed to assess serum levels of ceruloplasmin and Alkaline phosphatase in preterm and full-term delivery.
Materials and Methods: The present study includes total 80 subjects that comprise forty women presenting with preterm onset of labor followed by delivery and forty women who delivered at term served as controls. Blood Samples from the subjects were obtained for ceruloplasmin and Alkaline phosphatase estimation, when patient was in labor. Serum ceruloplasmin and alkaline phosphatase measured spectrophotometrically. Serum ceruloplasmin was estimated by Herbert A Ravin and Henry et al. method. Serum alkaline phosphatase was estimated by Kinetic p-NPP method.
Results: Serum ceruloplasmin levels were significantly increased (P<0.001) in preterm delivery as compared to full term delivery. Alkaline phosphatase levels are significantly increased in preterm delivery (p<0.001) as compared to full term delivery.
Conclusion: Our study showed that elevated levels of ceruloplasmin and alkaline phosphatase may be associated with preterm delivery in asymptomatic pregnant women. The elevated ALP may be

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due to mild chronic subclinical infection which may be responsible for preterm delivery. Ceruloplasmin is acute phase reactant, increased due to an antioxidant defence mechanism against oxidative stress.

Keywords: Preterm Birth (PTB); ceruloplasmin; alkaline phosphatase; full term delivery.

ABBREVIATIONS

PTB : Preterm birth;
PROM : Premature rupture of membrane;
PTL : Preterm labour;
ALP : Alkaline phosphatase;
HPLC : High performance liquid chromatography;
ELISA : Enzyme linked immunosorbant assay.

1. INTRODUCTION

Preterm birth, referring to all births before 37 completed weeks of gestation, is a major perinatal health problem because it is the leading cause of perinatal morbidity and mortality worldwide [1]. Frequency of PTB remains unchanged worldwide over two decades. Globally, every year, an estimated 15 million infants are born preterm [2].

Events leading to preterm birth are still not completely understood, although the etiology is thought to be multifactorial. It is, however, unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Causal factors linked to preterm birth include medical conditions of the mother or fetus, genetic influences, environmental exposure, infertility treatments, behavioural and socioeconomic factors and iatrogenic prematurity. Approximately 45–50% of preterm births are idiopathic, 30% are related to preterm rupture of membranes (PROM) and another 15–20% is attributed to medically indicated or elective preterm deliveries [3].

Preterm phenotypes were classified using a new conceptual framework based on severe maternal, fetal and placental conditions causally associated with preterm birth. Maternal causes include extrauterine infection, Clinical chorioamnionitis, Pre-eclampsia and eclampsia. Fetal causes comprise Fetal distress, Fetal inflammatory response syndrome, Multiple pregnancy, fetal anomaly. Placental causes contain early bleeding, Mid-/late-pregnancy bleeding [4]. Several single gene disorders have been associated with an increased risk of preterm birth [5].

There are several risk factors for preterm birth has been identified; the ability to specifically predict when labour will occur remains indefinable. The detection of novel biomarkers that could identify women who will consequently deliver preterm may allow for timely medical intervention and targeted therapeutic treatments aimed at improving maternal and fetal outcomes [6].

Serum and amniotic fluid C-reactive protein, serum ferritin, cervicovaginal fluid fetal fibronectin, cervical Phosphorylated form of insulin like growth factor binding protein-1(phIGFBP1), Salivary progesterone, serum relaxin, enzymes like Lactate dehydrogenase, Alkaline phosphatase, Corticotropin releasing hormone, serum serpin B7, dual biomarker model i.e. albumin/vitamin D-binding protein, serum ceruloplasmin etc have been reported to be associated with an increased incidence of preterm labor [1].

Alkaline phosphates-(ALP) are a group of isoenzymes produced by liver (isoenzymes ALP1-1), bones (isoenzymes ALP2), kidneys, small intestine and placenta (isoenzymes ALP-3). Placenta ALP is physiologically produced by placenta at the brush border membranes of the syncytiotrophoblast, and its' major function is thought to aid in metabolism and facilitate transport across cell membranes. It appears in maternal serum between the 15^{th} and the 26^{th} weeks and increases during the third trimester. Marked elevation of serum ALP may be caused by liver or bone pathology such as malignancy, extra hepatic biliary obstruction and intrahepatic cholestasis. Mild chronic infection of the placenta may be responsible for the markedly raised ALP level in pregnancy [7].

Ceruloplasmin, an acute phase serum protein has been reported to increase in cases of premature rupture of membrane (PROM) and during inflammation Ceruloplasmin is a α-2, copper transporting globulin synthesized in liver microsomes and possesses feroxidase activity. It acts as an antioxidant in serum by oxidizing ferrous iron which could otherwise act as a catalyst in generating toxic free radicals [8].

Most of the predictive biomarkers suggested for preterm delivery need methods like High performance liquid chromatography (HPLC), Chemiluminescence, Enzyme linked immunosorbant assay (ELISA), Immunoturbidometry etc. They are expensive and time consuming. However estimation of serum ceruloplasmin and alkaline phosphatase is the most affordable and widely available biomarkers. Therefore present study aimed to assess the levels of Ceruloplasmin and Alkaline phosphatase in full term delivery and preterm delivery.

2. MATERIALS AND METHODS

The present study is the prospective study, carried out in the Department of Biochemistry and Department of Obstetrics & Gynaecology MGM Medical College Navi-Mumbai. Ethical clearance was obtained for the present study. The subjects for the present study were enrolled from Department of OBGY MGM Medical College Navi-Mumbai. The present study includes total 80 subjects (Women with regular prenatal care) ranging age 18-40 years, which were divided into two groups: Control Group- 40 women with full term delivery Study Group - 40 women with preterm delivery (Women presenting with preterm onset of labor followed by delivery (regular, uterine contractions resulting in progressive cervical effacement and dilatation). Written consent has been taken from women with preterm and full term delivery.

5 ml of venous blood sample in plain vial was collected from the patients when patient was in labor, before the administration of any medications. Serum was separated and used for estimation of Alkaline Phosphatase and ceruloplasmin. Inclusion Criteria for preterm delivery was the pregnant women with less than 37 weeks of gestation. Inclusion Criteria for full-term delivery was the pregnant women with 38-42 weeks of gestation. Pregnant women having Maternal uterine anomalies, multi-fetal gestation, cervical cerclage, lethal fetal anomalies, preeclampsia, multiple pregnancies and diabetes mellitus were excluded from the study. Serum alkaline phosphatase was estimated by Kinetic p-NPP method by spectrophotometry using commercially available kit (Coral Clinical System). Serum ceruloplasmin was estimated by Herbert A and Ravin HA method by spectrophotometry [9].

3. RESULTS AND DISCUSSION

3.1 Results

The result indicates that mean levels of Ceruloplasmin were significantly increased in study group as compared to control group. ($p<0.001$) Mean levels of alkaline phosphatase were significantly increased in study group as compared to control group. ($p<0.001$).

3.2 Discussion

Preterm birth is a major obstetric and neonatal challenge and every preterm birth imposes a considerable burden on limited health care resources and is a main cause of mortality and morbidity for newborns. The most important causes of newborn death, in the world, were prematurity (80%) [10,11]. Various morbidities, largely due to organ system immaturity, are significantly increased in infants born before 37 weeks' gestation compared with those delivered at term [10].

Our results showed that a marked correlation of elevated Ceruloplasmin and Alkaline phosphatase levels in women with preterm delivery was observed when compared to women with full term delivery.

Ogino M et al. [12] showed that ceruloplasmin in cervicovaginal secretions was significantly higher in PROM cases ($p<0.001$) than non PROM cases and concluded that active ceruloplasmin in the cervicovaginal secretion might be a reliable clinical marker for term PROM.

Table 1. Comparison of mean levels of ceruloplasmin and alkaline phosphatase in control (Full term delivery) and study groups (Preterm delivery)

Parameters	Control group (Full term delivery) Mean±SD	Study group (Preterm delivery) Mean±SD
Ceruloplasmin mg/dl	37.35±20.28	55.44±20.63**
Alkaline phosphatase U/L	198.97±86.96	304.36±97.85**

*P<0.05 (significant), **p<0.001 (Highly significant)

Vitoratos N, et al. [13] have reported that the higher serum ceruloplasmin levels in patients with premature rupture of the membranes than those with preterm labor but intact membranes ($p<0.05$) as well as to non-labouring patients. They concluded that a loss of ferroxidase activity of ceruloplasmin in patients with rupture of the membranes and probably suggest a defect in the maternal defence mechanisms.

Kadota A, et al. [14] reported that the Mean serum ceruloplasmin at 22 weeks of those subjects who eventually developed preterm labour was found to be higher than those who did not develop preterm and this increase was found to be highly significant. ($p<0.0001$). The increased ferroxidase activity in PROM might be the compensatory rise in antioxidant defence mechanism as ferroxidase activity is a measure of antioxidant activity.

Kalra VB, et al. [15] reported that the serum levels of Ceruloplasmin were highest in the 3rd Trimester in PROM cases as compared to non PROM cases.

We found high mean levels of ceruloplasmin in preterm delivery as compared to full term delivery may be due to subclinical infection generated oxidative stress and inflammatory pathology. Ceruloplasmin increased as an antioxidant defence mechanism against oxidative stress.

In present study, we found alkaline phosphatase was significantly increased in preterm (study group) as compared to the full term (control). $p<0.001$ (Table 1).

Our results are concurrent with Singh B, et al. [16], Tripathi R, et al. [17], Meyer RE, et al. [18], Moawad AH, et al. [19], Huras H, et al. [20] and Goldenberg RL, et al. [21], Singh B, et al. [16] reported an increase in serum ALP during PTD. In opposition to that, Erdinc et al.[22] noted no correlation between serum ALP and PTD.

Tripathi R et al. [17] demonstrated that the significant correlation between preterm birth and serum ALP levels at 24-28 weeks was observed. ($P\leq 0.009$). Meyer RE et al. [18] found that increased alkaline phosphatase serum levels followed by a 6.8 times increased risk of preterm birth at the age of 32 weeks and 5.1 times at the age of 35 weeks.

Moawad AH et al. [19] reported association of alkaline phosphatase and alpha-fetoprotein levels with preterm birth. When alkaline phosphatase levels at 24 weeks were studied, the odds ratio for spontaneous preterm birth at <32 weeks was 6.8 and at <35 weeks was 5.1 they observed a significant elevation in ALP in pregnancies that ended in spontaneous preterm birth.

Huras H et al. [20] were found that significantly higher levels ALP (above 300 u/l) in patients from the study group with preterm delivery compared to the control group women without preterm delivery. Goldenberg RL et al. [21] demonstrated that a high ALP level was associated with three fold increased risk for preterm delivery.

The elevated alkaline phosphates level in pregnancy is due to increase in number of cells synthesizing it. However it is increased even more in preterm delivery because of increased wear and tear of placental cells. It also gives an idea that there must have been some injury to the placenta due to hypoxia leading to infarction of the placenta and therefore increases in the level of alkaline phosphatase in the maternal serum [23].

We found high level of alkaline phosphatase in preterm women's as compared to term women's due to the mild chronic subclinical infection which may be responsible for the markedly raised ALP level in preterm delivery.

4. CONCLUSION

Findings of this study demonstrated that the assessment of concentrations of Ceruloplasmin and Alkaline phosphatase can be used as suitable markers for predicting risk of preterm delivery. Moreover these parameters are cost effective, simple to perform and less time consuming and indicative of subclinical infections of pregnancy which could be one of the reasons for preterm delivery. On the other hand, our study has certain limitations which include smaller sample size of preterm cases and controls as its pilot study. Since preterm labour is multifactorial, various factors may have been unaccounted. A larger sample size research from early pregnancy at regular intervals is recommended to address the limitations.

CONSENT

All authors declare that written informed consent was obtained from the patient.

ETHICAL APPROVAL

All authors hereby declared that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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