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Original Research Article

Biomarkers for Preterm Delivery Prediction: A Hospital-Based Investigation

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Abstract

Introduction: One important factor that influences morbidity and newborn mortality is preterm delivery (PTD). Severe neonatal disease or even death is a risk for preterm newborns. One of the most serious risks to the developing baby and one of the unsolved issues in clinical obstetrics is preterm delivery (PTD); a predictive biomarker for this condition has to be found. Thus, the purpose of this research was to evaluate the blood concentrations of iron, ceruloplasmin, haemoglobin, and alkaline ferritin phosphatase in both preterm and full-term deliveries.

Materials & Methods: The study's sixty individuals are divided into thirty who presented with preterm labor and delivery and thirty who served as controls by giving birth at term. When a patient was in labor, blood samples were taken for the measurement of ceruloplasmin, iron, ferritin, and alkaline phosphatase.

Results: Comparing preterm delivery to full term delivery, there was a significant rise ($P \leq 0.05$) in serum alkaline phosphatase levels. Preterm delivery was associated with considerably higher serum ceruloplasmin levels than full-term delivery. ($P \leq 0.05$). Comparing preterm to full term birth, there was a substantial rise ($P<0.001$) in serum ferritin levels. Compared to full-term deliveries, preterm deliveries did not significantly raise serum iron levels. ($P \leq 0.05$).

Conclusion: Serum levels of alkaline phosphatase, ferritin, and ceruloplasmin rise significantly in preterm birth compared to full term delivery, suggesting that these biomarkers may be utilized as predictive indicators for preterm birth. These criteria are also inexpensive, easy to use, and time-efficient. They also show signs of subclinical pregnancy infections, which may contribute to preterm delivery.

Abbreviation: Preterm Delivery, Labor, ALP, HPLC, ELISA and Pregnancy.

Introduction

Any birth that occurs before the full 37 weeks of gestation is considered preterm. Worldwide, an estimated 15 million babies are born prematurely, primarily affecting low- and middle-income (LMIC) nations. [1] A term birth is defined as occurring between 37 and 42 weeks gestation, which is the best time for both mother and child to have a healthy outcome. Under the International Classification of Diseases, a term pregnancy is defined as a delivery occurring between 37 and 42 completed weeks of gestation, or 259–293 days. While there is a large range of gestational ages within which neonatal outcomes might vary, a 2012 international stakeholder working group recommended sub-categorizing term delivery to more precisely represent deliveries and their outcomes. [2] Around the world, preterm delivery is a leading cause of mortality as well as the long-term loss of human potential in survivors. Premature birth abnormalities account for 35 percent of the 3.1 million newborn deaths worldwide each year, making them the single greatest direct cause of neonatal mortality. [3] It is assumed that babies delivered before 28 weeks of pregnancy are severely preterm. The likelihood of a baby surviving decreases with early birth. Even those who survive occasionally experience serious, frequently chronic health issues and disabilities.

The "age" of pregnancy is known as gestational age, and it's commonly expressed in weeks and days. [4] preterm membrane rupture (PROM) accounts for thirty percent of preterm births, idiopathic causes account for forty to fifty percent, and medically recommended or voluntary premature delivery accounts for fifteen to twenty percent. [5] An earlier history of preterm spontaneous labor (PTL), cervical instability, infection, antepartum hemorrhage, and multimodal care are among the risk factors linked to early birth. Nonetheless, over 50% of women without identified risk factors will experience PTL and subsequent preterm birth. [6]

Ceruloplasmine is an acute phase serum protein that is generated in liver microsomes and contains feroxidase activity. It has been observed to rise in cases of premature membrane rupture (PROM) and to be an aα-2, copper carrying globulin during inflammation. By oxidizing ferrous iron, which may otherwise serve as a catalyst in the creation of harmful free radicals, it functions as an antioxidant in serum. [7]

ALPs are a class of isoenzymes that are produced by the kidneys, small intestine, liver (isoenzymes ALP1-1), bones (isoenzymes ALP2), and placenta (isoenzymes ALP-3). The principal role of placenta ALP, which is physiologically synthesized by the placenta at the brush border membranes of the syncytiotrophoblast, is believed to be to assist transport across cell membranes and aid in metabolism. Between weeks 15 and 26, it first manifests in maternal serum, and during the third trimester, its levels rise. [8]

One sign that has been investigated for the prediction of preterm labor is ferritin, an intracellular iron storage protein. [9] Ferritin is an acute phase reactant and it increases during inflammation. [10]

The requirement for iron is greater in rapidly growing and differentiating cells. [11] Poor birth weight and premature birth have been linked to poor iron status. Changes in stress hormones including norepinephrine, cortisol and corticotrophin-releasing hormone concentrations, and oxidative stress indexes are thought to be caused by iron deficiency and may have a negative impact on either or both fetal growth and gestation. [12] In poor nations with limited healthcare resources, iron prophylaxis during pregnancy need to be advised as a general prophylactic administered to all women. [13] Regardless of their current iron status, it is advised that all pregnant women take iron supplements as part of the prophylactic of general iron. Individual prophylaxis refers to modifying iron supplementation based on a woman's iron level. [14]

While a number of risk factors for preterm delivery have been identified, it is still impossible to pinpoint with precision when labor will begin. Finding new biomarkers that could identify pregnant women who would therefore give birth prematurely could open the door to prompt medical intervention and focused therapy interventions meant to enhance outcomes for both the mother and the fetus.

The majority of the predictive biomarkers that are recommended for preterm birth need techniques like as immunoturbidometry, chemiluminescence, enzyme linked immunosorbent assay (ELISA), and high-performance liquid chromatography (HPLC). They take a lot of time and money. Nonetheless, the most accessible and reasonably priced biomarkers include those that measure serum levels of ferritin, iron, alkaline phosphatase, and chromolluscemia. Thus, the purpose of the current study was to evaluate the levels of iron, ferritin, alkaline phosphatase, and cercoplasmin in both full-term and preterm deliveries.

Material and Method

The Department of Obstetrics and Gynecology conducted the current prospective study. For this particular investigation, ethical clearance was secured. The Department of OBGY provided the subjects for this study. Eighty women, aged 18 to 40, who receive regular prenatal care make up the total subjects in this study. They are split into two groups: 40 women in the control group gave birth at full term. Study Group: 40 preterm-delivery women (women presenting with regular, uterine contractions resulting in progressive cervical effacement and dilatation) who had preterm onset of labor and delivery. Women who delivered babies at full term as well as preterm have given their written approval.

Results

Table 1: Comparison of Mean Levels of Ceruloplasmin, Alkaline phosphatase, Iron and Ferritin in Control Group and Study Group.

Parameters	Control Group (Normal) Mean ±SD	Study Group (preterm) Mean ±SD
Ceruloplasmin mg/dl	40.15± 21.27	60.37± 20.59**
Alkaline phosphatase U/L	194.28± 83.41	312.71±99.57**
Iron µg/dl	52.06±8.29	55.68±10.67#
Ferritin ng/ml	16.82±12.87	70.12± 24.49**

**P<0.001 (highly significant), # p>0.05 (Not significant)

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. ($P<0.001$). The result indicates that mean levels of ferritin were significantly increased ($P<0.001$) in study group as compared to control group. The result also indicates that iron levels were increased but not statistically significant in study group as compared to the control group. ($P>0.05$).

Discussion

Worldwide, premature delivery is a leading cause of mortality as well as the long-term loss of human potential in survivors. Premature birth problems account for 35% of the 3.1 million newborn fatalities worldwide each year, making them the single greatest direct cause of neonatal deaths. In practically all high- and middle-income countries across the world, premature delivery is the primary cause of infant mortality. Premature birth raises a baby's risk of dying from other causes as well. Premature birth infections are thought to be a risk factor in at least half of all neonatal fatalities. [15] In 2010, over 10% of all newborns worldwide were born prematurely, leading to an approximate total of 14.9 million preterm births. Of those, over a million babies lost their lives directly as a result of their early birth. [16]

There was no discernible change in iron levels between the two groups in this investigation. Regarding serum ferritin, alkaline phosphatase, and ceruloplasmin levels, there was a statistically significant difference between the two groups. Our findings demonstrated a clear association between mothers who had babies before their due date and higher levels of ferritin, alkaline phosphatase, and cercoplasmin.

Ogino M et al. [17] 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. A. Kondhalkar et al. [18] Serum ceruloplasmin levels were significantly increased ($P<0.001$) in preterm delivery as compared to full term delivery. Kapil Bhatia et al. [19] found the higher ceruloplasmin level in the group who delivered before 34 weeks as compare to the group who delivered after 34 weeks.

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 defense 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 A. Kondhalkar [18] Alkaline phosphatase levels are significantly increased in preterm delivery ($p<0.001$) as compared to full term delivery. Tripathi R et al. [20] demonstrated that the significant correlation between Preterm delivery and serum ALP levels at 24-28 weeks was observed. (≤ 0.009). Moawad AH et al. [21] 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 delivery 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. [22] were found that significantly higher levels ALP (above 300 IU/L) in patients from the study group with preterm delivery compared to the control group women without preterm delivery. Goldenberg RL et al. [23] demonstrated that a high ALP level was associated with three fold increased risk for preterm delivery.

Pregnancy raises the amount of alkaline phosphates because more cells are producing it. However, due to enhanced placental cell deterioration, it is elevated even further in premature birth. It also suggests that there may have been placental damage from hypoxia, which resulted in placental infarction and elevated levels of alkaline phosphatase in the mother's serum. [24]

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.

In present study, we found mean levels of ferritin were significantly increased in preterm delivery (study group) as compared to the full term delivery (control). ($P<0.001$) (Table 1)

Our study is concurrent with study of Tamura T et al. [25] reported that women with higher serum ferritin concentrations, compared with those women with lower concentrations experienced an almost threefold increased risk of delivering preterm. Movahedi M et al. [26] showed that, on 222 singleton pregnancies, 69 (31.1%) had preterm delivery and 153 (68.9%) had term delivery). Women who delivered before 37 weeks had a higher mean serum ferritin concentration than those who delivered after 37 weeks of gestation (26.7 ± 5.5 ng/ml vs. 19.8 ± 3.6ng/ml, ($P <0.001$).

A vaginal pH shift that occurs during pregnancy can lead to a vaginal cervical infection. The

production of ferritin as a component of the acute phase response occurs after bacterial colonization and macrophage infiltration at the chorionic deciduas interface. Brailsford postulated that by promoting oxidative metabolism, the elevated extracellular ferritin plays a significant part in the host's defense against bacteraemia. Therefore, rather than being the result of iron overload, the elevated serum ferritin level in the study group is most likely an acute phase reaction to a subclinical infection. [27]

The notably elevated ferritin levels observed in preterm birth relative to full term delivery may be the result of subclinical infections. Ferritin is produced as a component of the acute phase response and is a member of the host defense system.

In present study, we found mean levels of iron was non-significantly increased in preterm (study group) as compared to the full term (control). ($P>0.05$) (Table 1)

Our study is concurrent with study of Allen LH et al [28] reported that there was no evidence to support a relationship between iron deficiency as cause of premature birth and low birth weight. Tripathi R et al [29] showed that serum iron levels were less in women who delivered preterm as compared to the women who delivered at term but the difference was not statistically significant ($P \geq 0.053$). Further they reported that in developing countries like India the etiology of Preterm deliverymight be more related to nutrition and specifically deficiency of micronutrients like iron. Kaneshige E et al [30] demonstrated that, the serum iron levels were higher in the study group (PROM) as compared to the control group (third trimester) although the difference was not statistically significant. The large variation in serum iron levels could be the cause of the lack of statistical significance. Nevertheless, a covert process of infection is known to boost serum iron as a result of tissue damage, which could account for this slight increase in study groups.

The lack of a statistically significant difference in iron levels between preterm and full-term deliveries may be caused by the large range of blood iron levels and daily fluctuations in serum iron. An individual's serum iron levels might change from day to day or even within a single day. Nonetheless, idiopathic infection, which causes tissue damage and may consequently cause a modest increase in iron levels, may be the cause of this non-significant increase in study groups.

Conclusion

The results of this study indicate that ferritin, alkaline phosphatase, and ceruloplasmine concentrations can be evaluated as suitable markers to estimate the risk of preterm delivery. These parameters also show subclinical pregnancy infections, which may be a contributing factor in preterm delivery, and are inexpensive, easy to use, and time-efficient. However, given that it is a pilot study, ours has some limitations, one of which being the smaller sample size of controls and preterm cases. Premature labor is multifaceted, meaning that some aspects might not have been taken into account. A larger sample size study from early pregnancy is advised at regular intervals in order to offset the disadvantages.

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