Section: Obstetrics and Gynaecology

Original Research Article

TO STUDY ALKALINE PHOSPHATASE LEVELS OF ANTENATAL PATIENTS AS A PREDICTIVE MARKER AND FETAL OUTCOME

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Abstract

Background: To study fetal outcomes in antenatal patients with singleton pregnancies with raised level of alkaline phosphatases and to see its role in predicting preterm deliveries, neonatal outcomes and NICU admission. **Materials and Methods:** Detailed information was given to all women enrolled in the study, and all the participants signed consent forms. Data was collected using format including detailed history and examination and test used in study. Age, parity, locality was documented for all pregnant women. Investigations i.e., blood examination, urine examination, liver function tests. Fetal outcomes (birth weight and NICU admissions) were recorded. The data was analysed statistically using student t test, Chi-Square test. ALP value less than 0.05 was considered statistically significant. **Result:** In our study we conclude that maximum subjects were of age group 21-30 years and maximum belongs to urban area. Maximum subjects were of 36–40-week Period of gestation and delivered at full term (76.1%). Maximum patients underwent LSCS (61.9%). The chi square test shows significant relationship between (Alkaline Phosphatase) ALP values and preterm birth and maternal complications and NICU admission of babies among subjects. **Conclusion:** The data from our study are consistent with the hypothesis that raised Alkaline Phosphatase can predict preterm deliveries and subjects with high ALP their babies are at risk. With increasing awareness, early suspicion of pregnancy-related liver disorder and immediate termination of pregnancy; maternal mortality due to these disorders can be reduced.

INTRODUCTION

The physiological changes in a pregnant woman can confuse the clinician by some nonspecific symptoms such as nausea, vomiting and abdominal pain hence need to be differentiated from pathologies which carry significant risk to the mother and her baby.

The pathological derangement in the liver functions may be related to pregnancy or may coexist with pregnancy and may be divided into three major groups. First group includes liver disorders that are specific to pregnancy such as hyperemesis gravidarum, pre-eclampsia, eclampsia, syndrome of haemolysis, elevated liver test and low platelets (HELLP), acute fatty liver of pregnancy and intrahepatic cholestasis of pregnancy. These disorders are mostly trimester specific. Second group includes intercurrent liver disease occurring during pregnancy such as viral hepatitis and herpes simplex. Maternal factors including parity, body composition and smoking are associated with changes in placental gene expression, indicating that the placental tissue responds to changes in the maternal environment. Maternal body composition has also been associated with changes in placental function which could affect fetal development. While evolutionary pressures on placental development are likely to favour adaptations that protect the fetus from maternal undernutrition, its ability to respond to maternal overnutrition are of increasing interest.[1-5]

Alkaline phosphatase (ALP) is an ubiquitous enzyme found in nearly every organ. The serum ALP consists of many distinct isoenzymes found in the liver, bone, placenta and less commonly, small

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intestine. ALP isoenzyme activity decreases to the normal level at about 20 weeks postpartum. In pregnancy, significantly elevated levels of serum ALP require careful investigation. Characterization by electrophoresis should be performed to determine the origin of ALP. Several studies suggest an association between elevated ALP activity and preeclampsia, low birth weight, prematurity, and placental insufficiency.[3-5]

During pregnancy, serum ALP levels increase significantly mainly due to the increased secretion of placental fraction. Accordingly, many studies have shown that placental ALP isoenzyme activity contribute to the increased serum total ALP in pregnant women. Furthermore, the increase of placental isoenzyme has been found to be significant at 31-38 weeks and at 38 weeks of gestation. However, the significance of these increases is still not very clear. Elevated activity of serum ALP levels were reported in gestational diabetes24, in an uncomplicated pregnancy, in growth retardation and in preeclempsia26. Furthermore, the Preterm Prediction Study reported an increased risk of spontaneous preterm birth in asymptomatic pregnant women with elevated ALP at 24 and 28 weeks.[2-6]

Although there are currently few reports describing abnormally high serum ALP in pregnancy, some studies have shown that this enzyme could be an obstetric and perinatal marker associated with preterm delivery, hypertensive disorders gestational diabetes, large for gestational age fetuses, and intrauterine growth restriction. The exact mechanism of this association remains unknown, but it is hypothesized it may be the result of placental insufficiency. It was described as an association between elevated ALP levels and placental damage from uteroplacental vascular disease, such as infarctions or chronic intervillositis. Nonetheless, there were studies that did not show any adverse perinatal outcomes with increased ALP levels.[3-6]

The present study was conducted to study maternal and fetal outcome in antenatal patients with raised Alkaline Phosphatase levels.

MATERIALS AND METHODS

The patients for the study, alkaline phosphatase levels of antenatal patients as a predictive marker and fetal outcome, were selected from the cases admitted to Department of Obstetrics and Gynaecology, RKDF Medical College, Bhopal from dec 2020-May 2022.

Study design/type: Clinical Descriptive Study.

Place of study: Department of Obstetrics and Gynaecology, RKDF Medical College, Bhopal Study Group: All Women admitted at Obstetrics and Gynaecology department at RKDF Medical College, Bhopal were selected for the study.

Study Duration: A 18month study from DEC 2020-MAY 2022

Inclusion Criteria

- All pregnant women coming to Department of Obstetrics and Gynecology
- Patients enrolled between 2nd and 3rd trimester were included.
- Women symptomatic of maternal complications (P.I.H. Gestational diabetes, Hyperemesis gravidarum)
- Patients who were willing to participate in the research.

Exclusion Criteria

- Multiple gestations and known congenital malformations
- Chronic hypertension
- Inflammatory bowel disease (IBD)
- Gall bladder disease
- Active bone disease (i.e., skeletal dysplasia, healing fracture)
- Active liver disease (ie., hepatitis, cholestasis, cholelithiasis (gallstones))
- Pre-existing type 1 and 2 Diabetes
- Early-onset IUGR
- Women not consenting to participate in the research.
- Sample size All pregnant women admitted at the Obstetrics and Gynaecology from DEC,2020-MAY, 2022

Study Variables

a. Independent variables: Age, Parity, Period of gestation, Locality.
b. Dependent variables: Pregnancy outcomes and complications, Mode of delivery, Fetal outcomes (fetal weight and NICU admissions).

Procedure

All women attending the Obstetrics and Gynecology department at RKDF Medical College, Bhopal from DEC, 2020-MAY,2022 were included in the study. Detailed information was given to all women enrolled in the study, and all the participants signed consent forms. Data was collected using format including detailed history and examination and test used in study. Age, parity, locality were documented for all pregnant women. Investigations i.e., blood examination, urine examination, liver function test, proteins, enzymes, HIV, HbsAg, VDRL or any other examination needed were performed. Maternal venous blood samples were collected in a plain bottle. The blood analyses were performed within 2 h of blood sampling using a hematology analyzer . Pregnancy outcomes and complications, route of delivery, fetal outcomes (birth weight and NICU admissions) were recorded.

RESULTS

In our study we conclude that maximum subjects out of 155 subjects were of age group 21-30 years and maximum belongs to urban area. Maximum

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subjects were of 36–40-week Period Of Gestation and delivered at full term (76.1%). Maximum patients underwent LSCS (61.9%). The chi square test shows significant relationship between ALP values and preterm birth and maternal complications and NICU admission of babies among subjects.

The data from our study are consistent with the hypothesis that raised Alkaline Phosphatase can predict preterm deliveries and subjects with high ALP are at high risk for maternal complications and there babies are at risk too. With increasing awareness, early suspicion of pregnancy-related liver disorder and immediate termination of pregnancy; maternal mortality due to these disorders can be reduced.

Statistical Analysis

The collected data was summarized by using frequency, percentage, mean & S.D. To compare the qualitative outcome measures Chi-square test or Fisher's exact test was used. The data was analysed statistically using student t test, Chi-Square test. A P value less than 0.05 was considered statistically significant. To compare the quantitative outcome measures independent t test was used. If data was not following normal distribution, Mann Whitney U test was used. SPSS version 22 software was used to analyse the collected data. p value of <0.05 was statistically significant.

Table 1: Relationship of Alkaine phosphatase [ALP] and parity

Alkaine phosphatase				
	HIGH		**LOW**	
MULTI	100	70.4%	116	69%
PRIMI	42	29.6%	52	31%
CHI SQUARE		2.60	.004	
P VALUE		.106	.944	

Table 2: Relationship of alkaline phosphatase [ALP] values and preterm and term delivery

	Preterm		**Term**	
N=110	**Frequency (n=74)**	**%**	**Frequency (n=236)**	**%**
High ALP	54	38%	88	62%
Normal ALP	20	11.9%	148	81.1%
CHI Square	14.49			
P value	<0.01			

Table 3: Relationship of ALP values and birth weight

Birth Weight	**High ALP**		**Normal ALP**	
	Frequency (n=142)	**%**	**Frequency (n=236)**	**%**
Low	34	24%	40	23.8%
Normal	108	76%	128	76.2%
CHI Square	.0003			
P Value	.984			

Table 4: Relationship of ALP values and NICU admission

NICU Admission	**High ALP**		**Normal ALP**	
	Frequency (n=142)	**%**	**Frequency (n=168)**	**%**
No	26	18.3%	90	53.6%
Yes	116	81.7%	78	46.4%
CHI Square	20.43			
P Value	<0.01			

DISCUSSION

Liver diseases in pregnancy although rare but they can seriously affect mother and fetus. Signs and symptoms are often not specific and consist of jaundice, nausea, vomiting, and abdominal pain. Although any type of liver disease can develop during pregnancy or pregnancy may occur in a patient already having chronic liver disease. All liver diseases with pregnancy can lead to increased maternal and fetal morbidity and mortality. It is difficult to identify features of liver disease in pregnant women because of physiological changes. Physiological changes of normal pregnancy can be confounding with that of sign and symptoms of liver diseases. Telangiectasia or spider angiomas, palmar erythema, increased alkaline phosphatase due to placental secretion, hypoalbuminemia due to hemodilution. These normal alterations mimic physiological changes in patients with decompensated chronic liver disease. Besides all these pathological changes however, blood flow to the liver remains constant and the liver usually remains impalpable during pregnancy. The diagnosis of liver disease in pregnancy is challenging and relies on laboratory investigations.[1-3]

Abnormalities of liver function (notably rise in alkaline phosphatase and fall in serum albumin) are common in normal pregnancy, whereas rise in serum bilirubin and aminotransferase suggest either exacerbation of underlying pre-existing liver disease, liver disease related to pregnancy or liver disease unrelated to pregnancy. Than N et al in their

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study postulated that pregnant women appear to have a worse outcome when infected with Hepatitis E virus. Liver diseases associated with pregnancy include abnormalities associated hyperemesis gravidarum, acute fatty liver disease, pre-eclampsia, cholestasis of pregnancy and HELLP syndrome. Prompt investigation and diagnosis is important in ensuring a successful maternal and foetal outcome. In general, prompt delivery is the treatment of choice for acute fatty liver, pre-eclampsia and HELLP syndrome and ursodeoxycholic acid is used for cholestasis of pregnancy although it is not licenced for this indication.[1,2]

The purpose of the study by Meyer RE et al was to determine whether elevated midtrimester serum placental alkaline phosphatase levels are predictive of preterm delivery. Women with placental alkaline phosphatase levels ≥2.0 multiples of the median were significantly more likely to be delivered of a preterm infant in the current pregnancy compared with women with levels <2.0 multiples of the median.It was concluded that women with elevated placental alkaline phosphatase levels are at increased risk for preterm delivery.[2]

The primary aim of this retrospective study that included women with pruritus and BA levels ≥10 μmol/L study by Brouwers L et al was to investigate the correlation between pregnancy outcome and bile acid (BA) levels in pregnancies that were affected by intrahepatic cholestasis of pregnancy (ICP). In addition, correlations between maternal and fetal BA levels were explored.The study group was divided in mild (10-39 μmol/L), moderate (40-99 μmol/L), and severe (≥100 μmol/L) ICP. Main outcome measures were spontaneous preterm birth, meconium-stained amniotic fluid, asphyxia, and perinatal death. Spontaneous preterm birth (19.0%), meconium-stained fluid (47.6%), and perinatal death (9.5%) occurred significantly more often in cases with severe ICP. Higher BA levels were associated significantly with spontaneous preterm birth Severe ICP is associated with adverse pregnancy outcome. Levels of BA correlate between mother and fetus.[3]

Jaundice affects a small percentage of pregnant women, yet it takes a major toll on health of both mother and fetus especially in developing countries like India. Jaundice in pregnancy carries a grave prognosis for both the fetus and the mother, and is responsible for 10% of maternal deaths. Krishnamoorthy J, Murugesan A et al studied and found out the effect of jaundice during pregnancy on maternal and fetal outcome. The most common cause of jaundice was Viral Hepatitis. Maternal mortality was 7.8%. The common maternal complications were atonic postpartum haemorrhage 9.8%, hepatic encephalopathy 7.87%, disseminated intravascular coagulation 5.88% and hepatorenal failure 4%. Perinatal mortality was 35.5%. Conclusions derived were that jaundice in pregnancy has adverse fetomaternal outcome. Improvement in health awareness, education and regular antenatal checkups, early referrals result in early diagnosis and treatment of jaundice during pregnancy thus reducing maternal and fetal mortality and morbidity.[4]

Sharma S et al did a prospective study on maternal and fetal outcome in jaundice complicating pregnancy All cases were in third trimester of pregnancy, 93.3% were unbooked, 73.3% were term, 60% were of lower socioeconomic status and 73.3% were urban. All patients presented with jaundice at time of admission. Pruritus was most common presenting symptom present in 60% of patients. Other presenting complaints were nausea, high BP, abdominal pain and petechiae. Viral Hepatitis was most important cause of jaundice in this study found in 46.7% of cases. Jaundice in pregnancy results in a very high perinatal as well as maternal morbidity and mortality, and requires an early diagnosis and careful management.[5]

Rajagambeeram R et al studied diagnostic utility of heat stable alkaline phosphatase in hypertensive disorders of pregnancy. Human placental alkaline phosphatase (PLAP), synthesized in placenta during pregnancy by placental syncytiotrophoblast, assumes diagnostic relevance.Study included pregnant women, 60 patients with hypertension and 60 controls. Biochemical assays were carried out by the IFCC approved procedures based on spectrophotometric method Serum heat stable ALP isoenzyme and PLAP/ALP ratio could be useful adjuvant markers in diagnosis of HDP in association with other relevant and economically viable biochemical tests.[6]

Lata I et al worked on diagnosis of liver disease in pregnancy is challenging and relies on laboratory investigations.The underlying disorder can have a significant effect on morbidity and mortality in both mother and fetus, and a diagnostic workup should be initiated promptly. If we see the spectrum of liver disease in pregnancy, in mild form there occur increase in liver enzymes to severe form, where liver failure affecting the entire system or maternal mortality and morbidity. It can not only complicate mother's life but also poses burden of life of fetus to growth restriction. Most of the times termination is only answer to save life of mother but sometimes early detection of diseases, preventive measures and available active treatment is helpful for both life. Extreme vigilance in recognizing physical and laboratory abnormalities in pregnancy is a prerequisite for an accurate diagnosis. This could lead to a timely intervention and successful outcome.[7]

Increased uric acid, gamma-glutamyl transpeptidase and alkaline phosphatase in early-pregnancy associated with the development of gestational hypertension and preeclampsia This was studied by Chen Y et al. A total of 1,041 pregnant women were enrolled in this prospective cohort study. Higher serum UA, GGT, ALP, and LDH levels, as well as lower eGFR and AST/ALT, were associated with higher BP levels during pregnancy and an increased

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risk of HDP. After adjustment for maternal age, pre-pregnancy BMI and other potential confounders, UA, GGT, ALP, and LDH remained positively associated with both BP and HDP. This study suggests that increased UA, GGT, and ALP in early-pregnancy are independent risk factors of gestational hypertension and preeclampsia.[8]

Liu Y et al studied that early elevated alkaline phosphatase increases the risk of large-for-gestational-age birth weight in pregnant women with normal glucose tolerance. The aim of this study was to assess the association between levels of alkaline phosphatase (ALP) in early pregnancy and the incidence of large-for-gestational-age (LGA) neonates in pregnant women without gestational diabetes mellitus. A significantly increased risk of LGA was associated with higher serum concentrations of ALP in pregnant women with NGT, even it is in normal reference range.[9]

Estiu MC et al studied relationship between early onset severe intrahepatic cholestasis of pregnancy and higher risk of meconium-stained fluid. The study included 382 pregnancies complicated by ICP managed at a referral. The patients were classified into three groups according to the severity of hypercholanemia at diagnosis; mild (10–19.9 μmol/L), moderate (20–39.9 μmol/L) and severe (≥40 μmol/L). Their clinical characteristics and pregnancy outcomes were investigated in a prospective observational study.The risk of MSAF is associated not only with the magnitude of hypercholanemia at diagnosis but also with the early gestational onset of raised maternal serum bile acids.[10]

CONCLUSION

In our study we conclude that maximum subjects out of 155 subjects were of age group 21-30 years and maximum belongs to urban area. Maximum subjects were of 36–40-week Period Of Gestation and delivered at full term (76.1%). Maximum patients underwent LSCS (61.9%). The chi square test shows significant relationship between ALP values and preterm birth and maternal complications and NICU admission of babies among subjects.

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A proactive approach is mandatory to improve investment in health care by including LF.T. as a routine investigation to prevent maternal complications and early elevated maternal ALP should not be ignored as it has physiological and pathological significance and there is an urgent need to increase awareness about this preventable cause of maternal death all over India.

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