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Full length Research Article

Serum Human Placental Lactogen Assays in Ultrasound Evaluated Pregnancy-Induced Hypertension; A Marker of Placental Function in Pregnancy

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Summary: Human placental lactogen (HPL) is a pregnancy-related hormone produced by the placenta. The overall functions of serum HPL impacts the developing fetus and placenta. The objective of this study was to determine the relationship between maternal serum concentration of HPL and sonographic fetal growth parameters in pregnancy induced hypertension as a marker of placental function. This prospective cross-sectional study was conducted over a 9-month period in the University of Calabar Teaching Hospital, Calabar, Nigeria that involved 100 women with pregnancy induced hypertension. An obstetric ultrasound scan was done on all the subjects and their blood was collected for HPL evaluation using Enzyme-linked Immunosorbent Assay (ELISA). ANOVA and Pearson's correlation were used to analyze the data. Maternal serum HPL had a significant positive correlation with PLA (P=0.000), EGA (P=0.000), EFW (P=0.000) and AFI (P=0.000) and a significant negative correlation with Proteinuria (P=0.047), FHR (P=0.032) and HC/AC (P=0.000). It is concluded that maternal serum HPL concentration increases as pregnancy advances and causes a significant increase in placental thickness, fetal weight and amniotic fluid volume, however, its reduction is significantly associated with the onset of pre-eclampsia, fetal distress and asymmetrical intra-uterine growth restriction. Thus, the evaluation of maternal serum HPL concentration is a reliable marker of placental function in the second half of pregnancy.

Keywords*: Human Placental Lactogen, Placenta, Fetal weight, Pregnancy induced hypertension, Pre-eclampsia, Intrauterine growth restriction*

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INTRODUCTION

Human placental lactogen (HPL) is synthesized in a progressively increasing amount by the syncytiotrophoblast and extravillous trophoblast of placenta. It is coded by the genes HPL-3 and HPL-4 within the human growth hormone variant (HGH-V) gene locus and regulates the expression of placental function (Garay *et al*., 2022; Durkovic and Mandic, 2009). Its level usually rises to between 5 and 7 micrograms at term, more than any other peptide hormone (Garay *et al*., 2022). HPL is detected as early as the 5th week of gestation in the maternal circulation and its production is not affected by stress or metabolic changes (Wilde and Oakey, 1975; Velegrakis *et al*., 2017). The serum concentration of HPL is usually low in early pregnancy but increases with the advancement of pregnancy, showing some correlation with placental weight. The overall action of the hormone, HPL, impacts on the fetus and the mother (Durkovic and Mandic, 2009; Reis *et al*., 2002).

Human placental lactogen is an important hormone of pregnancy and the most highly expressed peptide hormone of the placenta. It is actively involved in the physiological changes of the maternal metabolic process which favours a sustained increase in lipolysis that frees fatty acids for increased glucose supply to the fetus and placenta. HPL also increases maternal appetite, decreases the urge for maternal activities and drives metabolic adaptations throughout the course of pregnancy. In addition, it stimulates the production of insulin-like growth 1 (IGF-1) which is an important growth factor in the third trimester of pregnancy, stimulates DNA synthesis and acts as an insulin antagonist (Garay *et al*., 2022; Durkovic and Mandic, 2009; Bersinger and Ødegård, 2004; Yu *et al*., 2022).

Some studies have reported associations between subnormal levels of HPL and pregnancy complications such as intra-uterine growth restriction (IUGR), reduced fetal weight, threatened abortion, bleeding, placental calcification, fetal distress, intra-uterine fetal death, gestational diabetes and reduced maternal caregiving behaviour. Furthermore, low serum HPL has been reported to be associated with high level of maternal anxiety during pregnancy which could result in adverse maternal outcome such as elevated blood pressure and possibly gestational hypertension and pre-eclampsia. All these are evidence that normal levels of circulating HPL is requisite for an ideal pregnancy with a healthy mother (Garay *et al*., 2022; Durkovic and Mandic, 2009; Jeckel *et al*., 2018; Thomas, 2022).

Placental insufficiency encompasses several conditions in which the placenta does not function adequately to maintain optimal conditions for the developing fetus and this includes the secretion of subnormal concentrations of HPL into the maternal circulation (Jeckel *et al*., 2018; Manokhina *et al*., 2017). The measurement of maternal serum HPL concentration is a rapid means of determining pregnancies that might be in immediate danger and require hospital care and those with apparently healthy pregnancies (Wilde and Oakey, 1975). This is extremely beneficial to the Obstetrician as it aids the monitoring of pregnant women especially those with high-risk pregnancies (Durkovic and Mandic, 2009). Therefore, maternal serum HPL should be regarded as a valuable marker of placental function or insufficiency (Durkovic and Mandic, 2009; Reis *et al*., 2002; David and Spencer, 2022).

There is a dearth of data on studies of maternal serum levels of HPL in pregnancy induced hypertension and its effect on the growing fetus and placenta in this locality. We aimed to evaluate the relationship between maternal serum concentration of HPL and sonographic fetal growth parameters in pregnancy induced hypertension as a marker of placental function.

MATERIALS AND METHODS

Study design: This is a prospective cross-sectional study that was conducted in the Radiology Department, Obstetrics and Gynecology Department and Chemical pathology Department of the University of Calabar Teaching Hospital, Calabar, Nigeria. The duration of the study was from January 2019 to September 2019. The study population was obtained from the women who attended the antenatal clinic (ANC) of the Obstetrics and Gynecology Department of the University of Calabar Teaching Hospital, Calabar. Prior to the commencement of this study, approval was obtained from the health research ethics committee of the University of Calabar Teaching Hospital, in strict compliance with the Helsinki Declaration. The protocol number assigned to this study by the ethical committee was UCTH/HREC/33/329. Purposive sampling technique was employed for the research.

This study involved 100 subjects with singleton pregnancies between 20 and 40 weeks who had pregnancy induced hypertension (PIH). A subset of 71 subjects had gestational hypertension and another subset of 29 subjects had pre-eclampsia (proteinuria superimposed on gestational hypertension). The following were the exclusion criteria; Multiple gestation, gestational diabetes, sickle cell disease, human immune-deficiency virus (HIV), tuberculosis, congenital anomaly and chronic hypertension.

Procedure: After the routine antenatal tests and examinations were done by an Obstetrician, informed consents were obtained from the participants and they were each requested to fill the questionnaire. The subjects were made up of pregnant women with a blood pressure reading of ≥140/90 mmHg with or without a coexisting proteinuria. Proteinuria was determined by the use of urine dip sticks. The subjects with gestational hypertension (GH) were categorized into three groups.

- Mild GH = 140 – 159 mmHg for the systolic blood pressure and 90 – 99 mmHg for the diastolic blood pressure.
- Moderate GH = 160 – 179 mmHg for the systolic blood pressure and 100 – 109 mmHg for the diastolic blood pressure.
- Severe GH = ≥ 180 mmHg for the systolic blood pressure and ≥ 110 mmHg for the diastolic blood pressure.

The results obtained from the blood pressure measurements, body mass index assessment, socio-demographics and urine tests for protein of the subjects were recorded as data for this study.

Ultrasound procedure: Each subject was brought into the ultrasound suite of the Radiology Department of the University of Calabar Teaching Hospital, Calabar, by a female chaperon and appropriately positioned for the procedure. There was a head pillow on the couch to ensure comfort for the subjects. The ultrasound machine utilized for the study was an Aloka prosound SSD–3500sx (a 2-Dimensional device with Doppler facility) that has a curvilinear transducer with a frequency range of 3.5 - 5MHz (manufactured in 2008 by Aloka company limited located in Meerbusch, Germany). An ultrasonic gel was applied by the Radiologist and with a gentle motion of the transducer on the abdominal surface the fetuses were examined. The fetal anthropometric parameters were measured and these included Bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and the femur length (FL). HC/AC ratio was calculated by dividing the value of HC by the value of AC obtained from the measurements of the fetal body parts. The scanning duration for each subject was approximately 15 minutes. The entire ultrasound procedures were done by two experienced Radiologists. Estimated gestational age (EGA), estimated fetal weight (EFW), fetal heart rate (FHR) and HC/AC were recorded as data for this study. HC/AC > 1.2 signified asymmetrical intrauterine growth restriction (Peleg *et al*., 1998).

Amniotic fluid index (AFI) is derived by mentally dividing the pregnant abdomen into four quadrants by using the umbilicus as the reference point. The linea nigra divides the abdomen into left and right halves while a horizontal line that traverses the umbilicus separates the uterus into upper and lower halves. The four sonographic measurements were summed to obtain the AFI in cm. Oligohydramnios refers to an amniotic fluid index below 5cm (Efanga *et al*., 2023). The measured value of AFI for each subject was recorded as data for this study.

The plane of measurement of the placental thickness is a perpendicular line drawn from the point of insertion of the umbilical cord at the chorionic membrane of the echogenic placenta to its basal membrane. This measurement is usually done during periods of maternal relaxation and the absence of myometrial contractions (Efanga and Akintomide, 2020). The measured value of the placental thickness for each subject was recorded as data for the study.

Serum HPL evaluation procedure: The subjects were ushered into the laboratory of the Chemical Pathology Department of the University of Calabar Teaching Hospital, Calabar, for the HPL analysis. The specimen collection procedure was meticulously explained to the subjects prior to venepuncture. They were in the sitting position and well-rested for 20 minutes before blood collection from the antecubital vein was done. Four millilitres (4mls) of venous blood were collected into plain non-anticoagulated sample bottles for the HPL quantitative evaluation. The blood was allowed to clot. The clotted blood specimen was centrifuged at 3000 rpm for 5 minutes. The supernatant serum was then harvested and transferred to storage tubes and stored at -20 0C for a maximum of one week before batch analysis. Quantitative analysis was done using Enzyme-linked Immunosorbent Assay (ELISA). The microwell reader automatically plotted a standard curve of absorbance of the standards over their respective concentrations. The HPL values of the maternal serum samples were obtained from the standard curve (Human Placental Lactogen ELISA kit insert from Biovendor: Biovendor Laboratorni Medicina a.s, Karasek, Brno, Czech Republic). The maternal serum concentration of HPL for each subject was recorded as data for this study.

Statistical analysis:
The data obtained from the research was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). Appropriate descriptive and inferential statistical methods were used to analyse the data while tables and a bar chart were the means of displaying the results where applicable. One-way analysis of variance (ANOVA) test was done. Correlation was determined by using Pearson's correlation and P value < 0.05 was considered statistically significant.

RESULTS

The age of the 100 subjects involved in the study was from 16 to 39 years with a median of 32 years. The mean value of BMI was 34.03±6.56 kg/m2 which shows that the subjects were generally obese. HPL ranged from 1.80 to 8.54 microgram/ml with a mean value of 6.30±0.21 microgram/ml. The mean value of systolic blood pressure and diastolic blood pressure were 156±22.02 mmHg and 99.68±11.49 mmHg respectively. The mean value of proteinuria was 0.58±1.02. The mean EFW was 2.23±1.07 kg with a range of 0.37 to 4.77 kg while the mean PLA was 29.85±5.71 mm with a range of 15.65 to 38.60 mm. Majority of the subjects were married (67%), had secondary education (43%) and were employed (71%) (Table 1).

HPL was shown to have a significant positive correlation with PLA (P=0.000), EGA (P=0.000), EFW (P=0.000) and AFI (P=0.000) and a significant negative correlation with Proteinuria (P=0.047), FHR (P=0.032) and HC/AC (P=0.000). Both systolic (P=0.091) and diastolic (P=0.882) blood pressure were not significantly correlated with HPL (Table 2).

Table 1:
Socio-demographic characteristics of the subjects

Variables		F	Min	Max	Mean	SD
Age (years)		100	16.00	39.00	30.87	±5.02
BMI (kg/m^2)		100	18.90	63.00	34.03	±6.56
SYS (mmHg)		100	140.00	280.00	156.83	±22.02
DIA (mmHg)		100	90.00	160.00	99.68	±11.49
PROTEINURIA		100	0.00	3.00	0.58	±1.02
HPL (microgram/ml)		100	1.80	8.54	6.30	±0.21
Marital Status	**Single**	34				
	Married	67				
Educational Level	**Primary**	21				
	Secondary	43				
	Tertiary	36				
Employment Status	**Employed**	71				
	Unemployed	29				
EGA (weeks)		100	20.43	40.43	32.82	±5.40
EFW (kg)		100	0.37	4.77	2.23	±1.07
FHR (beats/min)		100	118.00	158.00	141.49	±8.69
HC/AC		100	0.90	1.30	1.04	±0.07
AFI (cm)		100	1.60	20.10	14.74	±3.33
PLA (mm)		100	15.65	38.60	29.85	±5.71

AFI – Amniotic fluid index; BMI – Body mass index; DIA – Diastolic blood pressure; EFW – Estimated fetal weight; EGA – Estimated gestational age; FHR – Fetal heart rate; HC/AC – Head circumference to abdominal circumference ratio; HPL – Human placental lactogen; PLA – Placental thickness; SYS – Systolic blood pressure. F = Frequency; Min = Minimum, Max = maximum.

Table 2:
Correlation of maternal serum HPL with the variables of the subjects (n=100)

Variables	Correlation Coefficient ®	P Value
AGE (years)	-0.140	0.165
BMI (kg/m2)	+0.062	0.539
SYS (mmHg)	-0.170	0.091
DIA (mmHg)	+0.015	0.882
PROTEINURIA	-0.200	0.046*
EGA (weeks)	+0.967	0.000*
EFW (kg)	+0.945	0.000*
FHR (beats/min)	-0.217	0.032*
HC/AC	-0.725	0.000*
AFI (cm)	+0.761	0.000*
PLA (mm)	+0.868	0.000*

(*) – P value < 0.05 is significant; AFI – Amniotic fluid index; BMI – Body mass index; DIA – Diastolic blood pressure; EFW – Estimated fetal weight; EGA – Estimated gestational age; FHR – Fetal heart rate; HC/AC – Head circumference to abdominal circumference ratio; PLA – Placental thickness; SYS – Systolic blood pressure.

Majority of the subjects were in the no proteinuria group (71%), while proteinuria +, proteinuria ++ and proteinuria +++ were made up of 10%, 9% and 10% of the subjects respectively. The mean HPL in the subjects gradually reduced from 6.48±0.24 (SEM) microgram/ml in no proteinuria to 5.54±0.64 (SEM) microgram/ml in +++ proteinuria (Figure 1). The highest mean HPL was in the

mild GIH group (6.67±1.99microgram/ml) while the least was in the moderate GH group (5.70±2.26 microgram/ml). The difference in the mean values of the three groups was not significant (P=0.110) (Table 3).

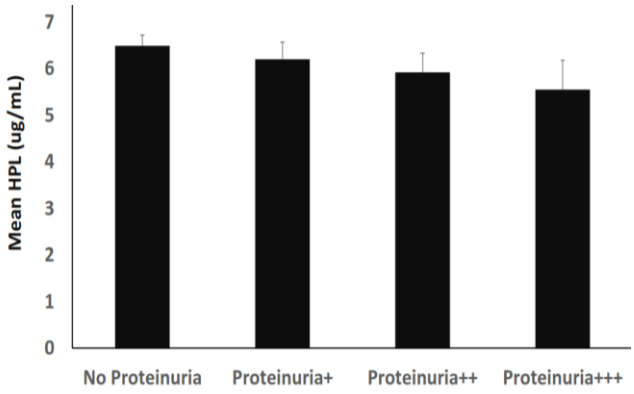

Figure 1:
Variation of mean **and standard error of mean** HPL serum concentration with the degree of proteinuria.
HPL – Human placental lactogen

Table 3:
HPL values in the GH groups

Degree of GH	n	Min µg/ml	Max µg/ml	Mean µg/ml	SD	P
Mild GH	63	1.80	8.51	6.67	±1.99	
Moderate GH	14	2.27	8.46	5.70	±2.26	
Severe GH	23	1.80	8.51	6.34	±2.08	0.110

P value – ANOVA P value; GH – Gestational hypertension; SD – Standard Deviation

DISCUSSION

The maternal serum concentration of HPL in the PIH subjects of this study was found to increase in direct proportion with the advancement of pregnancy between the 20th week to the 40th week of gestation. This association between HPL and EGA was noted to be significant (P=0.000). Our findings are in consonance with Durkovic *et al*. (2009) in Serbia, who observed that HPL increased in a linear fashion with the gestational age. McIntyre *et al*., (2000) further buttressing this fact, realized that the mean value of maternal serum concentration of HPL noted at the 28th week of gestation was increased by 69% at the 36th week of gestation. Pedersen *et al*. (1995) who evaluated HPL in maternal blood samples obtained between the 8th and 14th week of gestation found out that high levels of maternal serum HPL within this period was indicative of better fetal growth in the remainder of pregnancies. Serum HPL measurement is alleged to give information about the estimated gestational age in the first trimester of pregnancy, which could be useful in situations or locations where ultrasound services are unavailable (Sibiak *et al*., 2020).

Estimated fetal weight was observed to increase in the same manner as the maternal serum concentration of HPL did in this study. This positive correlation was found to be significant (P=0.000). In the same vein, McIntyre *et al*. (2000) reported that a significant positive correlation existed between HPL and fetal weight (P<0.001). Even in studies where maternal serum HPL were assayed at 32 weeks and 36 weeks of gestation, carried out by Higgins *et al*. (2012) and Knopp *et al*., (1985) a significant correlation between estimated fetal weight was observed with maternal serum HPL (at 32 weeks, P=0.02 and at 36 weeks, P=0.03). Still in congruence with this study, Seppala *et al*. (1970) noted that there was a significant positive correlation between maternal serum HPL concentration assayed ten days before delivery with fetal weight. In variance with our findings, Singer *et al*. (1970) found out from sampled maternal serum at birth following 50 deliveries that there was no correlation between fetal weight and HPL.

We demonstrated that HC/AC ratio had a significant negative correlation with maternal serum HPL concentration (P=0.000) which implies that an elevation of HC/AC ratio above 1.2 (that is indicative of asymmetrical IUGR) is associated with low levels of maternal serum HPL. This same trend was reflected in Bersinger *et al*.'s (2004) study that had only Scandanavian participants, who realized that maternal serum concentrations of HPL remained persistently low in IUGR fetuses as pregnancy advanced. Mittal *et al*. (2007) noted that the serum level of HPL in IUGR was lower than its value in normal pregnancy but the difference between both serum concentration was not significant (P<0.05). The evaluation of HPL can be used in the assessment of the risk for IUGR (Sibiak *et al*., 2020). However, it was reported by Kastrup *et al*. (1978) that HPL (obtained in the third trimester) was found not to correlate with fetal growth in-utero and after delivery, which differed from this study.

Spellacy *et al*. (1972) inferred after measuring the maternal serum levels of over 1000 women who had various complications of pregnancy that maternal serum HPL had no significant correlation with fetal heart pattern. However, this study revealed that maternal serum HPL was significantly correlated with FHR (P=0.032) in a negative manner such that a reduction in serum HPL likely provokes fetal tachycardia. Nevertheless, Spellacy *et al*. (1972) further stated that maternal serum concentration of HPL was of no assistance in the selection of pregnant women who needed biophysical monitoring and that it had no correlation with fetal neurological development. Thus, they insisted that there was no evidence that the use of serial HPL assays improved perinatal survival. However, Dutton *et al*. (2012) discovered that there was a significant reduction in the circulating maternal serum HPL in women whose fetuses exhibited grossly reduced movement and those who had adverse perinatal outcome, further corroborating the relevance of serial HPL assay in pregnancy.

There was no significant relationship between maternal serum concentration of HPL with the blood pressure of the subjects in this study. The highest amount of maternal serum HPL concentration in the subjects with gestational hypertension was 6.67±1.99 micrograms/ml and this was observed in the mild stage of gestational hypertension and reduced afterwards in the moderate stage of gestational hypertension. In contrast, Spellacy *et al*. (1971) observed that mean maternal serum concentration of HPL in mild gestational hypertension was lower than its value in moderate and severe gestational hypertension.

Pre-eclampsia (proteinuria superimposed on gestational hypertension) was lucidly demonstrated to exhibit a

significant negative correlation with maternal serum levels of HPL (P=0.047) in this study. It was further observed that the mean HPL in the subjects consistently decreased in value as the degree of pre-eclampsia increased. Garay *et al*. (2022) had reported that low serum HPL was associated with high level of maternal anxiety during pregnancy which could result in adverse maternal outcome such as pre-eclampsia. Similarly, it was reported by Wilde *et al*. (1975) that the mean maternal serum HPL concentration in normal pregnancies was higher than its level in pre-eclampsia. Also, Durkovic *et al*. (2009) in Serbia, equally inferred that HPL mean value in pre-eclamptics was lower (2.07±1.75mg/l) than its value in normal pregnancy (4.15±2.55mg/l). The detection of normal levels of circulating maternal HPL within the first trimester in serial assays does not necessarily portend a healthy second half of a pregnancy as was discovered by Sifakis *et al*., (2011) who reported that the subsequent development of pre-eclampsia in their subjects had been preceded by normal levels of maternal serum HPL concentrations in the first trimester.

Incongruent with our findings, Mittal *et al*. (2007) observed that maternal serum concentration of HPL was significantly lower in normal pregnancy compared to pre-eclampsia with the median value of normal pregnancy noted to be 12, 157 pg/ml while that of pre-eclamptics was 23, 076 pg/ml ($P < 0.05$), but when SGA was superimposed on pre-eclampsia, the value of serum HPL reduced to that of normal pregnancy. They postulated that the high maternal circulating levels of HPL seen in women with pre-eclampsia was possibly a compensatory mechanism geared towards preserving the fetus and a failure of this mechanism results in the development of SGA.

Appropriate development of the placenta necessary for it to meet up with the continuously increasing need of the developing fetus is achieved by an adequate circulating concentration of maternal HPL through the stimulation of IGF-1 production to induce placental cell proliferation and increase maternal blood flow to the placenta (Sibiak *et al*., 2020; Burton *et al*., 2016). Placental thickness in this study was observed to have a significant positive correlation with maternal serum HPL (P=0.000). In agreement with this study, Rasie *et al*. (2022) reported that maternal serum HPL concentration is positively related to placental thickness ($P<0.05$). In addition, Higgins *et al*., (2015) who conducted a study that had 77 subjects with normal pregnancy outcome (NPO) and 23 subjects with adverse pregnancy outcome (APO) observed that the placental length, placental weight, placental thickness and placental volume were significantly lower in APO than NPO ($P<0.0001$). Fresh placental tissues from subjects with APO had less HPL compared to its content in the placentas of those with NPO. The median value of HPL in NPO was 27.0 mg/mg while its value in APO was 10.7 mg/mg and the difference was significant (P=0.006). In an animal-based research, Jeckel *et al*. (2018) observed a reduction in the placental weight of HPL deficient pregnancies (88.1±10.31 g in HPL deficient pregnancies vs 105.5±4.42 g in pregnancies with normal HPL concentration) but the difference was not significant (P=0.110). In contrast, Higgins *et al*. (2012) inferred that there was no significant correlation between maternal serum HPL and placental weight.

Pregnant women with oligohydramnios are regarded to be at an increased risk of perinatal morbidity. In addition, women who have borderline AFI (AFI between 5 and 10 cm) have a two-fold increase in the frequency of adverse perinatal outcome. The evaluation of AFI is essential to improve the determination of high-risk pregnancies (Voxman *et al*., 2002). In this study, maternal serum concentration of HPL in the subjects was shown to have a significant positive correlation with AFI (P=0.000). Indicating that the assessment of maternal serum HPL concentration mirrors the intrauterine status of the amniotic fluid. Oligohydramnios and borderline oligohydramnios have been found to be associated with adverse effects such as IUGR, fetal distress, congenital anomalies and perinatal mortality (Madaan *et al*., 2015). Healy *et al*, (1985) in a move to illuminate the relationship between both, postulated that the human chorionic laeve in a developing pregnancy has HPL receptors on its surface that are exclusively bound to by HPL which consequently affects amniotic fluid volume and in the index study it might appear that when the maternal serum HPL concentration reduces, the binding sites for the hormone becomes incompletely occupied and this likely reduces amniotic fluid production.

The study did not take into cognizance the ethnic or regional variations that were inherent in subjects who reside in other climes but were merely traversing the city and as such the results may be heterogenous and probably applicable in other regions of the world. Future studies in this district should distinguish and relate the data obtained in the evaluation of serum HPL of pregnant subjects from diverse ethnicities or nationalities for any form of significance. A larger sample size would have been more representative of the HPL associations with fetal growth parameters, intra-uterine amniotic fluid volume and intra-uterine placenta in pregnant women within this locality. The small sample size was the limitation of this study. Future studies should employ a larger sample size which should be utilized to produce a maternal serum HPL concentration nomogram chart for pregnant women in this locality.

In conclusion, maternal serum HPL concentration increases as pregnancy advances and causes a significant increase in placental thickness, fetal weight and amniotic fluid volume, however, its reduction is significantly associated with the onset of pre-eclampsia, fetal distress and asymmetrical intra-uterine growth restriction. Thus, the evaluation of maternal serum HPL concentration is a reliable marker of placental function in the second half of pregnancy.

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