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ORIGINAL RESEARCH ARTICLE

Role of Maternal Serum Human Placental Lactogen in First Trimester Screening

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Abstract The most preferred antenatal screening test is first trimester dual test which has a detection rate of 95% for foetal chromosomal anomaly. Maternal serum free β human chorionic gonadotropin (free β hCG) and pregnancy associated plasma protein A are used in first trimester dual test along with maternal demographic and foetal sonographic indices to calculate risk for foetal aneuploidy. Human placental lactogen is a placental hormone that is present in maternal serum only during pregnancy and its level rises in relation to the growth of the foetus and placenta. The objectives of this study was to measure and correlate maternal serum hPL with free β hCG, maternal age, maternal age related risk ratio and calculated risk ratio of first trimester screening. After obtaining permission from the Institutional Ethics Committee, hPL and free β hCG were measured from the serum of 84 pregnant women aged 20–40 years in 11–13th weeks + 6 days of gestation who underwent dual test during their antenatal check-up. Independent t test, Pearson's correlation, Spearman's correlation, Mann–Whitney U test, ANOVA were used wherever appropriate. A significant positive correlation between maternal serum hPL, maternal age related aneuploidy risk ratio (p value < 0.001) and aneuploidy risk ratio at the time of delivery (p value < 0.001) was observed. Also maternal age was negatively correlated with maternal serum hPL (p value < 0.001) and positively correlated with maternal serum free β hCG (p value 0.023). A significant negative correlation between maternal serum hPL and free β hCG (p value < 0.001) was found. To conclude low level of maternal serum hPL in advanced maternal age may reflect decreased functional syncytiotrophoblast mass which may predispose to adverse pregnancy outcome. As chance of baby born with chromosomal anomaly is known to increase with advancing maternal age, hPL may have role in first trimester screening.

Keywords First trimester dual test · Human placental lactogen · Free β hCG · Maternal age related risk ratio · Risk ratio at the time of delivery

Introduction

Various antenatal screening tests that are available for detection of chromosomal aneuploidy. These screening tests includes invasive and non-invasive procedures. Invasive diagnostic procedures carry a high risk for the mother and foetus due to their invasive nature. Non-invasive methods have added value compared to invasive being less likely to harm the mother and foetus. Non-invasive tests includes dual tests (maternal serum free beta hCG and PAPP-A) done in 1st trimester, triple test and quadruple test in 2nd trimester [1].

Early information about chances of a baby born with certain chromosomal aneuploidy like trisomy 21, trisomy 18, and trisomy 13 given by dual tests, along with details of maternal prenatal scanning (Nuchal translucence and crown rump length) and maternal demographic characteristics like age, height, weight, race, history of smoking/alcoholism, intake of folic acid etc. to calculate a risk ratio at the time of delivery (using a software) for probability of

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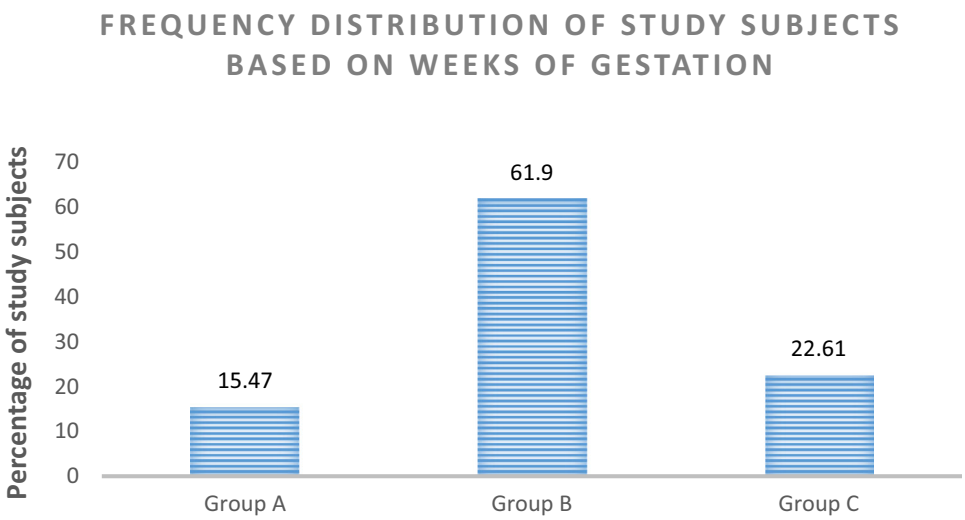

Fig. 1 Frequency distribution of study subjects

Table 1 Comparison of serum hPL and MoM of serum free β hCG levels among subjects in different weeks of gestation

Parameters	Group A (n = 13) (11th week)	Group B (n = 52) (12th week)	Group C (n = 19) (13th week)	*p* value
hPL (μg/ml) Mean ± SD	2.10661 ± 0.829	2.36448 ± 0.593	2.49963 ± 0.619	0.236* NS
MoM of Free β hCG (IU/L) Median and IQR	0.99 (0.64,1.73)	0.91 (0.61,1.58)	1.04 (0.70,1.59)	0.77** NS

MoM multiple of median, *IQR* inter quartile range, *NS* not significant

*ANOVA

**Mann–Whitney U test

Table 2 Comparison of serum hPL and MoM of serum free beta hCG levels among subjects in different age groups

Parameters	Group 1 (n = 59) (21–30 years)	Group 2 (n = 25) (31–40 years)	*p* value
hPL (ng/ml) Mean ± SD	2.52427 ± 0.537	1.9560 ± 0.705	< 0.001*
MoM of Free β hCG (IU/L) Median and IQR	0.89 (0.58,1.59)	1.10 (0.65,1.52)	0.765 NS#

NS not significant

*Independent t test

#Mann–Whitney U test

baby born with one of these above mentioned chromosomal aneuploidy is performed between the 11–13th weeks + 6 days of gestation. This first trimester dual test can detect 95% of foetal chromosomal aneuploidy [2].

Different softwares that are available to calculate the risk of chromosomal aneuploidy are Screening software [3–7] etc. A risk ratio less than 1:250 using Screening software for Down windows lab (SSDWL) is considered as high risk for foetal aneuploidy [8].

Free β hCG, a potent marker of first trimester screening, is also secreted from the syncytiotrophoblast of the placenta helps to maintain corpus luteum till 6 weeks of pregnancy [2]. Human placental lactogen (hPL), also known as human chorionic somatomammotropin (HCS) is a polypeptide hormone secreted from the syncytiotrophoblast of the placenta [9]. hPL is present only during pregnancy, with maternal serum levels rising in relation to the growth of the foetus and placenta. In maternal serum, hPL is first detected during 3rd week of gestation. The level rises steadily from 5 to 25 μg/mL till 36 weeks of gestation [2]. hPL promotes transfer of glucose and amino acids to the foetus and also helps to develop foetal vasculature. It has been seen that, in case of trisomy 21, its level decreases [10].

Table 3 Correlation of free β hCG with maternal age, maternal age related risk and risk at the time of delivery

Parameter	r value	*p* value*
Maternal age (years)	0.248	0.023#
Maternal age related risk ratio	− 0.28	0.01
Risk ratio at the time of delivery	− 0.602	< 0.001
Risk ratio at the time of delivery in Group 1 (n = 59)	− 0.634	< 0.001
Risk ratio at the time of delivery in Group 2 (n = 25)	− 0.490	0.013

NS not significant

#Pearson correlation

*Spearman correlation

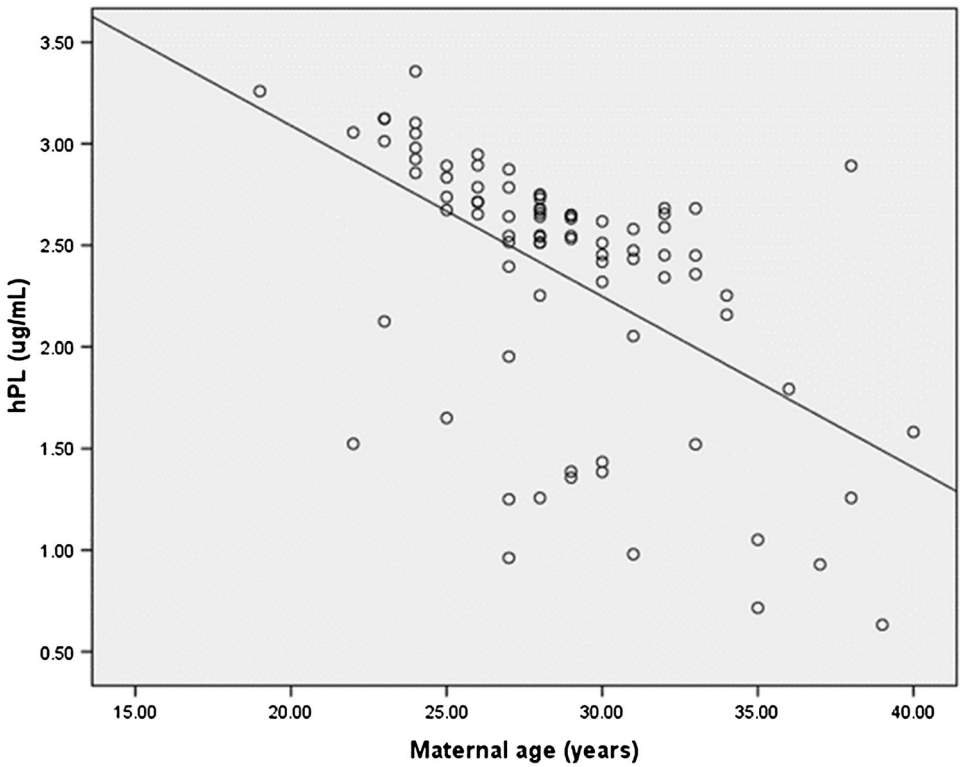

Fig. 2 Correlation of maternal serum hPL with maternal age (r = − 0.54, *p* = < 0.001)

Since free beta hCG and hPL are secreted from the syncytiotrophoblast, the main aim of this study was to correlate the two.

First trimester dual test does not take into account serum hPL. So, this study correlated serum hPL with maternal age and risk ratio generated by software SSDWL in pregnant women.

Materials and Methods

This cross sectional study was carried out in a tertiary care hospital after obtaining approval (IEC No 437/2013) from the Institutional Ethics Committee. Pregnant women aged 20–40 years in 11–13th +6 days of gestation who underwent dual test during their first trimester antenatal check-up were selected for this study (n = 84). Pregnant women with previous history of gestational diabetes, with disorders requiring long term medications and women with twin pregnancy were excluded from this study.

Grouping of study subjects based on gestational age:

Group A Pregnant women at 11–12th weeks of gestation
Group B Pregnant women at 12–13th weeks of gestation
Group C Pregnant women at 13–14th weeks of gestation

Grouping of study subjects based on age (in years):

Group 1 21–30 years
Group 2 31–40 years

Serum free β hCG was measured in Roche COBAS 6000 autoanalyzer. hPL was measured by specific ELISA kit made by Cusabio (catalog number: CSB-E09665 h).

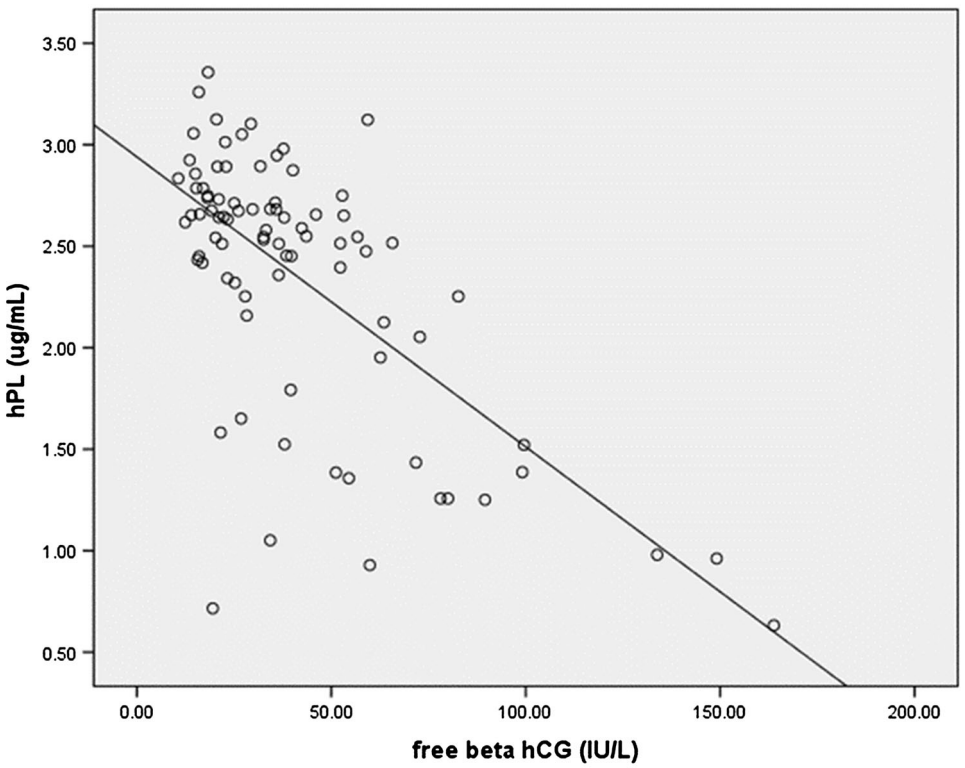

Fig. 3 Correlation of maternal serum hPL with free β hCG (r = − 0.544, $p = < 0.001$)

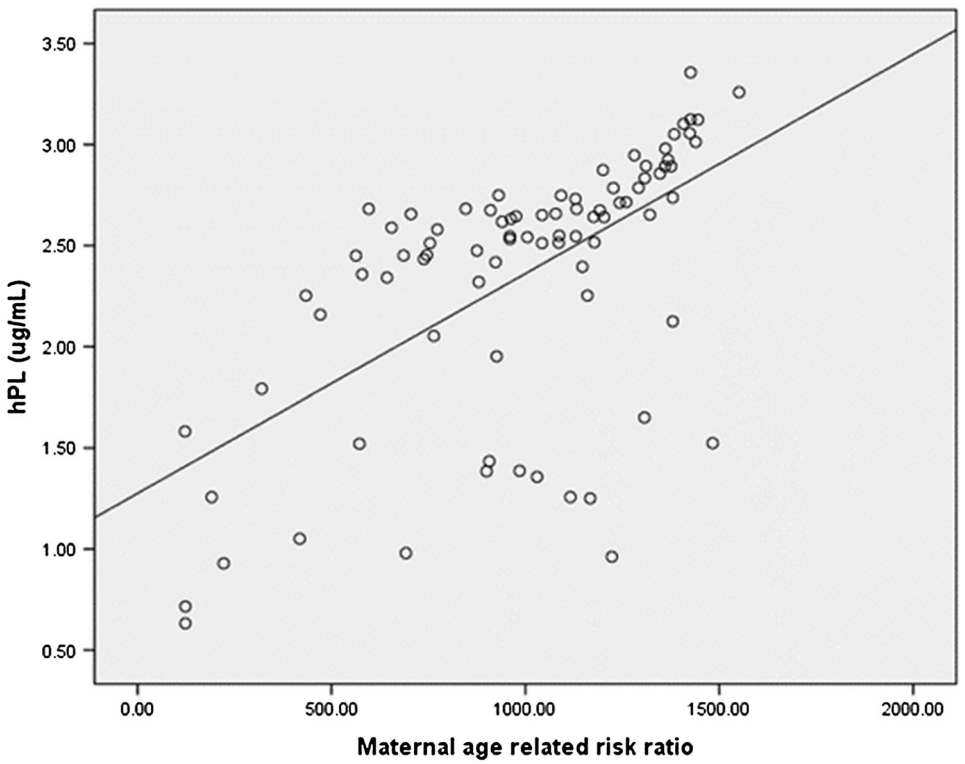

Fig. 4 Correlation of maternal serum hPL with maternal age related risk ratio (r = 0.66, $p = < 0.001$)

Statistical analysis: Data were compiled and statistical analysis was done using Independent t test, Mann–Whitney U test, Pearson's correlation, Spearman's correlation, ANOVA wherever appropriate.

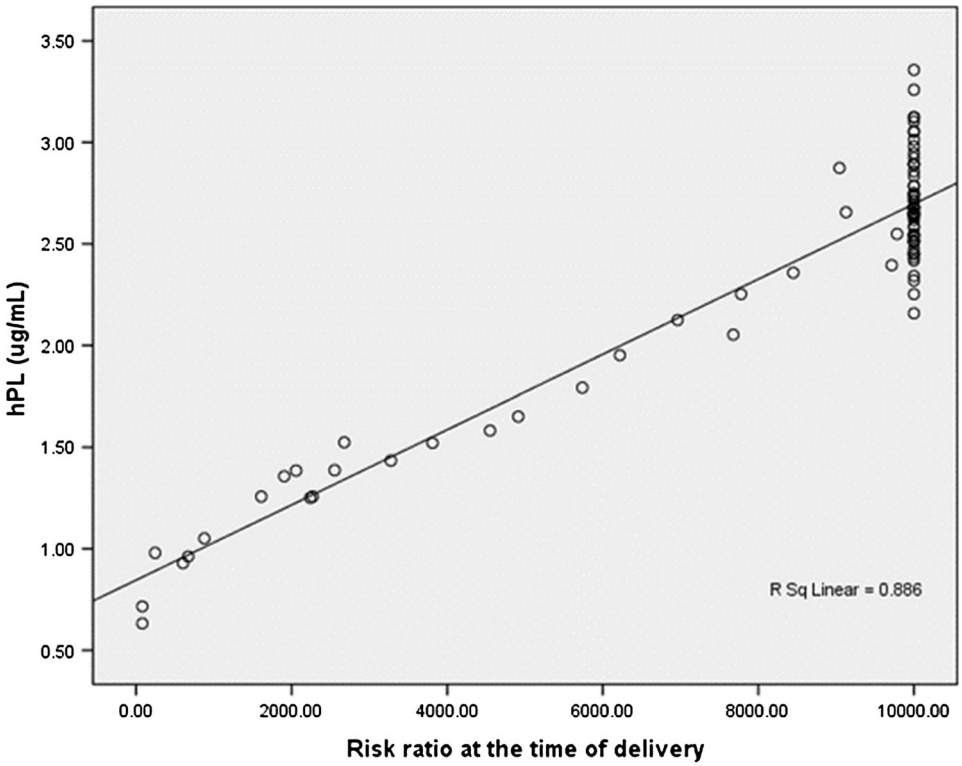

Fig. 5 Correlation of maternal serum hPL with aneuploidy risk ratio at the time of delivery (r = 0.754, $p = < 0.001$)

Calculation for risk assessment was done using Screening Software for Downs Windows Lab (SSDWL) made by SBP software and recommended by American College of Obstetricians and Gynaecologists (ACOG) [8]

Result

Majority of patients underwent screening test in the 12–13th week of gestation (Fig. 1).

Discussion

In the present study total of 84 pregnant women underwent first trimester screening and majority of pregnant women were in the 12–13th week of gestation (Fig. 1). Serum hPL and serum free β hCG levels were measured among subjects in different weeks of gestation and there was no significant difference in the levels, validating the reason for choosing this period for dual test (Table 1). Higher serum hPL was observed in later weeks of gestation (though *p* value was not significant) supporting role of hPL in fetal growth. This is also shown by a study by Christiansen [11].

Free beta hCG helps to sustain the growing foetus until 10th week and serum hPL plays a role in growth and development of foetus, their levels may be affected by advancing age and can affect the pregnancy outcome [12]. In this study however no significant difference in MoM of serum Free β hCG levels between two age groups but serum hPL was significantly low in higher age group (Table 2).

A significant positive correlation between maternal serum free β hCG with maternal age related risk was observed (Table 3). Whereas, a significant negative correlation between maternal serum hPL with maternal age was observed (Fig. 2). According to Browne [13], placental insufficiency in advanced maternal age could be a contributor for low levels of serum hPL.

There was a negative correlation of free β hCG with serum hPL, since free β hCG is involved in the maintenance of corpus luteum whose function is taken over by placenta leading to a decline in free β hCG. Human placental lactogen (hPL) level rises in maternal serum in relation to growth of foetus and placenta [12] (Fig. 3).

Significant positive correlation of maternal serum hPL with maternal age related risk and aneuploidy risk at the time of delivery was observed (Figs. 4, 5). This indicates low levels of hPL significantly correlated with higher maternal age related risk and can predispose to high foetal aneuploidy risk implying its prognostic value.

Maternal serum free β hCG showed a significant positive correlation with maternal age and a significant negative correlation with age related risk ratio and aneuploidy risk ratio at the time of delivery indicating higher levels of maternal serum free β hCG can predispose to high

aneuploidy risk for foetus (Table 3) Recent studies has shown that synthesis of β chain is the rate limiting step in hCG synthesis. Out of six, four recognized hCGβ genes are located in placenta. It is now thought that, hCGβ5 and hCGβ3 genes expressed in the placenta [14] are mainly responsible for the regulation of hCG synthesis [15]. So elevated β hCG mRNA observed in cases of foetal aneuploidy, is due to enhanced promoter activity of these genes. This leads to an increased secretion of free β hCG [16].

Conclusion

Low levels of maternal serum hPL correlated with higher age, maternal age related risk ratio and risk ratio at the time of delivery. It has a potential to be included in antenatal screening to further improve its specificity and sensitivity.

Limitations and Recommendations

Due to time limitations, parameters used in this study could not be compared with pregnancy outcome. Type of ovulation (induced or normal) and type of conception (natural or assisted) was not considered in this study.

This study can be extended in a larger number of patients to ascertain as to whether addition of hPL to the existing risk calculation algorithm can help in better and earlier detection of foetal aneuploidy.

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Compliance with Ethical Standards

Conflict of interest Dr. Indranil Ghoshal has received ICMR MD thesis grant. We declares that there is no conflict of interest.

Ethical Approval This study was conducted after obtaining ethical committee approval from institutional ethics committee Kasturba Hospital Manipal University Manipal (IEC437/2013).

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