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TO STUDY THE ASSOCIATION BETWEEN MATERNAL SERUM HOMOCYSTEIENE LEVEL IN PREGNANCY WITH PRETERM LABOR

Obstetrics & Gynaecology

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ABSTRACT

BACKGROUND AND OBJECTIVE: Preterm birth is one of the leading causes of perinatal mortality and morbidity and has also been dubbed as the single largest direct cause of neonatal deaths. Therefore, estimating the likelihood of spontaneous preterm delivery (sPTD) is essential to provide the best clinical interventions that may improve neonatal outcome.

METHODOLOGY: An prospective cross sectional study was done on 205 pregnant women between 14 – 27 weeks of gestation in Swaroop Rani Nehru hospital and Kamla Nehru Memorial hospital, Department of Obstetrics and Gynaecology, Prayagraj over a period of one year from September 2019 to September 2020.

RESULT: The area under the ROC curve (AUROC) for S. Homocyesteine (µMol/L) predicting Pre-Term Labor was 0.864 (95% CI: 0.806 - 0.922), thus demonstrating good diagnostic performance.At a cutoff of S. Homocyesteine (µMol/L) ≥9.87, it predicts Pre-Term Labor with a sensitivity of 78%, and a specificity of 94%. The area under the ROC curve (AUROC) for S. Homocyesteine (µMol/L) predicting Early vs Late preterm labor was 0.502 (95% CI: 0.379 - 0.626), thus demonstrating poor diagnostic performance.

INTERPRETATION AND CONCLUSION: This study showed significant association of serum homocysteine estimation between 14 – 27 weeks of gestation with preterm labor with good diagnostic accuracy while not much diagnostic significance was found in differentiating early vs late preterm labor.

KEYWORDS

Preterm labor, Serum homocysteine, Perinatal mortality, Perinatal morbidity

INTRODUCTION

Preterm birth is one of the leading causes of perinatal mortality and morbidity and has also been dubbed as the single largest direct cause of neonatal deaths. Preterm delivery accounts for 75-90% of neonatal and prenatal mortalities and serves as the main cause of short- and long-term neonatal defects. Despite decades of research into the causes of preterm birth, the biological causes of preterm birth remain largely unknown. Therefore, estimating the likelihood is essential to provide the best clinical interventions that may improve neonatal outcome and save valuable resources. The diagnostic significance of the available methods for assessing the likelihood of sPTD are limited, therefore; new markers are required to identify precisely pregnant women who have a high risk of preterm birth.***(Clements,Barfield, Ayadi& Wilber 2007)*****[1]**

Homocysteine is an amino acid which has sprung into prominence in the past few decade.It is recognized as an indiactor of risk of cardiovascular disorders, neurodevelopmental disorders ,pregnancy complications and adverse neonatal outcomes.Its serum levels during normal pregnancy showed biphasic pattern as it declines during first trimester, achieves the minimum in the second trimester and then shows slight increase towards the end of pregnancy.**(Murphy et al. and Dodds et al)[2].**The increased homocysteine level is suggested to cause preterm labor through induction of placental vascular endothelial dysfunction that induces inflammatory , hormonal , cellular effects that hasten the sequence of events ending in preterm labor.This postulated mechanism is supported by increased prevalence of decidual vasculopathy and accelerated villous maturation among women with hyperhomocysteinemia.Experimental studies revealed that moderately elevated homocysteine concentrations (16–24 uMmol/l) may induce cytotoxic and oxidative stress, leading to endothelial cell impairment.**(Wang et al)[3]**

METHODOLOGY

The present study was an analytical **prospective cross sectional study** done on 205 pregnant women between 14 – 27 weeks of gestation attending outpatient department in Swaroop Rani Nehru hospital and Kamla Nehru Memorial hospital, Department of Obstetrics and Gynaecology, Motilal Nehru Medical College, Prayagraj over a period of one year from September 2019 to September 2020

INCLUSION CRITERIA

1. Those women who are willing to participate
2. Women with singleton pregnancy
3. Gestational age between 14-27 weeks of gestation

EXCLUSION CRITERIA

1. Pregnant women with multiple gestation, malpresentations ,preterm premature rupture of membranes, active labor, diagnosed cervical insufficiency,
2. Uterine or fetal congenital abnormalities,Placenta praevia, IUGR ,oligo/polyhydroamnios, infectious or inflammatory diseases
3. Fetal distress as diagnosed by fetal cardiac tocography or fetal Doppler indices.
4. Medical problems like hypertensive disorder of pregnancy, anaemia,gesational diabetes or medically indicated preterm delivery

Written and informed consent was taken from all subjects prior to carrying out any study related procedure .Detailed history was taken regarding age, address, education, occupation, socioeconomic status, gravida, parity, period of gestation, duration of marriage, period of infertility, any kind of pelvic infection, smoking status, previous history of Preterm delivery and complications during present and past pregnancy like pregnancy induced hypertension, diabetes mellitus, APLA, intra uterine death, abruption and hepatitis and general, systemic and obstetrical examination was done. Routine antenatal blood and urine investigations were sent alongwith serum homocysteine .Venous blood samples was taken after overnight fasting for serum homocysteine estimation by chemiluminescence assay technique using a well calibrated fully automated chemiluminescence assay system between 14 – 27 weeks of gestational age.Women were followed up monthly till 28 weeks and then biweekly till 37 weeks then weekly till delivery.

In our study, early preterm labor was defined as onset of labor between 28 to 34 weeks of gestation and late preterm labor was defined as onset of labor between 34 to 37 weeks of gestational age. Stastical significance was set at 95% confidence interval (p value of less than or equal to 0.05).Continuous data were summarised as Mean ± S.D. while discrete (categorical) data in number and percentage.

RESULTS

Out of 205 antenatal patients, 37 patients went into early preterm labor, 51 into late preterm labor, 91 delievered at term, 7 were post term and 19 patients were lost to follow up(excluded from the study).

Table No.I: Distribution of the Patients According To Gestational Age at Blood Sampling for Serum Homocysteine(in Weeks) (n = 186)

Gestational Age at Sampling	No. Of Patients	Percentage
14-18 Weeks	38	20.4%
19-23 Weeks	101	54.3%
24-27 Weeks	47	25.3%
Total	186	100.0%
Mean±S.D	21.04±3.32	

38(20.4%) of the patients had Gestational Age at Blood Sampling: 14-18 Weeks. 101(54.3%) had 19-23 Weeks and 47(25.3%) had 24-27 Weeks. The mean (SD) of Gestational Age at Blood Sampling (Weeks) was 21.04 (3.32) and ranged from 14 – 27 weeks.

Table No. II: Distribution of the Patients According To Pre-Term Labor (n = 179)

Pre-Term Labor	No. Of Patients	Percetage
Present	88	49.2%
Absent	91	50.8%
Total	179	100.0%

Out of 179 antenatal patients, 88(49.2%) patients went into preterm labor while 91(50.8%) were delivered at term.

Table No.III: Distribution of the Patients According To Type of Pre-Term Labor (n = 88)

Type of Pre-Term Labor	No. Of Patients	Percentage
Early	38	43.2%
Late	50	56.8%
Total	88	100.0%

Out of 88 antenatal patients who went into preterm labor, 38(43.2%) of the patients had Early Preterm labor while 50(56.8%) of the patients had Late Preterm labor pain.

Table No. IV: Distribution Of Patients According To Serum Homocysteine Levels(n=179)

S. Homocysteine	No. Of Patients	Percentage
Normal(<5uMmol/L)	105	58.7%
High(>5uMmol/L)	74	41.3%
Total	179	100.0%
Mean±S.D	9.88±7.77	
P value	<0.001	

***post term = 7 and lost to follow up = 19 patients excluded from study**

Out of 179 antenatal patients, 105(58.7%) had serum homocysteine levels less than 5uMmol/L while 74(41.3%) had serum homocysteine levels more than 5uMmol/L.Serum Homocysteine (µMmol/L) was not normally distributed (Shapiro-Wilk Test).The p value was = <0.001 which was significant. The mean (SD) of Serum Homocysteine (µMmol/L) was 9.88 (7.77) and ranged from 2.98 - 31.98uMmol/L.

Table no V: comparison of the 2 subgroups pre-term vs term according to s. Homocysteine (µmmol/l)

S. Homocysteine (µMmol/L)	Pre-Term Labor		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	15.36 (7.43)	4.59 (2.91)	6919.000	<0.001
Range	3.27 - 31.98	2.98- 20.97		

The mean (SD) of S. Homocysteine (µMmol/L) in the Pre-Term group was 15.36 (7.43) while the mean (SD) of S. Homocysteine (µMmol/L) in the Term group was 4.59 (2.91) The S. Homocysteine (µMol/L) in the Pre-Term group ranged from 3.27 - 31.98 while the S. Homocysteine (µMol/L) in the Term group ranged from 2.98 - 20.97. There was a significant difference between the 2 groups in terms of S. Homocysteine (µMol/L) (W = 6919.000, p = <0.001).

The Box-and-Whisker plot below depicts the distribution of S. Homocysteine (µMol/L) in the 2 groups. The middle horizontal line represents the median S. Homocysteine (µMol/L), the upper and lower bounds of the box represent the 75th and the 25th centile of S. Homocysteine (µMol/L) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for S. Homocysteine (µMol/L) in each of the groups.

Figure No I: Box and Whisker plot of association between Preterm labor and Serum Homocysteine levels

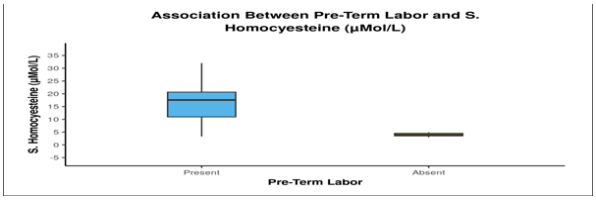

Table No. VI:- Serum Homocysteine As A Biomarker In Preterm Vs Term Group

Parameter(Serum Homocysteine) Preterm Vs Term	Value (95% CI)
Cutoff (p value)	≥ 9.87 (<0.001)
AUROC	0.864 (0.806 - 0.922)
Sensitivity	78.4% (68-86)
Specificity	94.5% (88-98)
Positive Predictive Value	93.2% (85-98)
Negative Predictive Value	81.9% (73-89)
Diagnostic Accuracy	86.6% (81-91)
Positive Likelihood Ratio	14.27 (6.04-33.69)
Negative Likelihood Ratio	0.23 (0.15-0.34)
Diagnostic Odds Ratio	62.46 (22.19-175.81)

The area under the ROC curve (AUROC) for S. Homocysteine (µMol/L) predicting Pre-Term Labor was 0.864 (95% CI: 0.806 - 0.922), thus demonstrating good diagnostic performance. It was statistically significant (p = <0.001). At a cutoff of S. Homocysteine (µMol/L) ≥9.87, it predicts Pre-Term Labor with a sensitivity of 78%, and a specificity of 94%. The odds ratio (95% CI) for Pre-Term Labor when S. Homocysteine (µMol/L) is ≥9.87 was 58.48 (20.87-163.86). The relative risk (95% CI) for Pre-Term Labor when S. Homocysteine (µMol/L) is ≥9.87 was 4.94 (3.38-7.45).

Table No.VII:-serum Homocysteine As A Biomarker In Early Vs Late Preterm Group.

Parameter(Serum Homocysteine) Early Vs Late Preterm Labor	Value (95% CI)
Cutoff (p value)	≤ 4.92 (0.973)
AUROC	0.502 (0.379 - 0.626)
Sensitivity	26.3% (13-43)
Specificity	82.0% (69-91)
Positive Predictive Value	52.6% (29-76)
Negative Predictive Value	59.4% (47-71)
Diagnostic Accuracy	58.0% (47-68)
Positive Likelihood Ratio	1.46 (0.66-3.24)
Negative Likelihood Ratio	0.9 (0.71-1.13)
Diagnostic Odds Ratio	1.63 (0.59-4.52)

The area under the ROC curve (AUROC) for S. Homocysteine (µMol/L) predicting Early vs Late preterm labor was 0.502 (95% CI: 0.379 - 0.626), thus demonstrating poor diagnostic performance. It was not statistically significant (p = 0.973).

DISCUSSION

Homocysteine, a sulphur containing amino acid, is recognized as an indicator of the risk of cardiovascular disorders, neurodevelopmental conditions, pregnancy complications and adverse neonatal outcomes.***Lopez et al.(2003)[4]*** reported significant lower levels of Hcy throughout pregnancy compared to those of non pregnant controls. The current study showed significant higher levels of maternal serum Hcy in preterm compared with the term delivery groups.These conclusions are supported by the findings of other authors although the evidence is weak. ***Kramer et al.(2009)[5]*** **and** ***Qiu et al.(2017)[6]*** proved that sPTD was correlated with elevated maternal serum Hcy level during the second and third trimesters, however; ***Knudtson et al. (2004)[7]*** failed to prove such association.

Vollset et al. (2000)[8] in their large Norwegian study showed significantly higher maternal Hcy levels few years following conception in women with history of preterm labor. However,

Ronnenberg et al.(2002)[9] showed an association between elevated preconceptional Hcy level and preterm birth in a study conducted on 29 Chinese women with preterm birth. These findings attract the attention to the possible role of increased Hcy level in the pathogenesis of preterm labor. The increased Hcy level was suggested to cause preterm labor through induction of placental vascular endothelial dysfunction that induces inflammatory, hormonal or cellular (e.g., increased gap junctions) effects that instigate or hasten the sequence of events ending in preterm labor. This postulated mechanism is supported by increased prevalence of decidual vasculopathy and accelerated villous maturation among women with hyperhom ocysteinemia. Also, an in vitro study demonstrated that Hcy enhanced the rate of spontaneous contraction of myometrium isolated from human pregnant uterus.

The current study showed that serum Hcy level is a supportive biomarker for prediction of preterm birth. However, there are no available persuasive findings derived from larger studies for comparison because Hcy has not been extensively evaluated in biomarker trials of complicated pregnancies other than preeclampsia.

CONCLUSION

It was an analytical prospective sross sectional study with an aim to study the association between maternal serum homocysteine level in pregnancy with preterm birth.This study showed significant association of serum homocysteine estimation between 14 – 27 weeks of gestation with preterm labor with good diagnostic accuracy while not much diagnostic significance was found in differentiating early vs late preterm labor.Improvement can only be achieved if obstetricians can reliably identify women at risk of preterm labor allowing for timely intervention**.**The ideal predictive test for preterm delivery should have sufficient sensitivity and specificity to ensure identification of women who will benefit from treatment of preterm labor.As clinicians move towards more biomarkers during pregnancy to assess risk of Preterm Birth, *hyperhomocysteinemia* may turn out to be a useful component of biomarker risk profile.

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