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Plasma Homocysteine Levels as a Predictor of Pre-Eclampsia in Pregnancy

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Introduction

Elevated plasma homocysteine levels have a role in placental vascular disease and are associated with pre-eclampsia. Raised levels during pregnancy can be associated with complicated maternal or foetal outcome with increased incidence of neural tube defects, placental abruption and infarction or intra-uterine growth retardation[1,2]. Identified causes for hyper-homocysteinaemia are: nutritional, such as: inadequate intake of vitamin B12;,B6 and folate; and mutations in the gene responsible for the enzyme MTHFR (methylene tetrahydrofolate reductase)[3]. Normal plasma homocysteine levels are 5-15 µmol/L. MTHFR is one of the key enzymes in the metabolism of homocysteine. The mutation leads to substitution of valine with alanine. Individuals who have homozygous C677T mutation exhibit decreased specific activity and increased thermolability of this enzyme which leads to increased plasma level of homocysteine.

Aims and Objectives

We aimed to determine whether the plasma homocysteine concentration in pregnancy is a predictor of development of pre-eclampsia. Secondarily, we aimed to correlate the variant MTHFR gene, smoking, vitamin B12 levels and folate levels with plasma homocysteine levels.

Methods

Data from 203 pregnant women recruited prospectively from antenatal clinics between 2004 and 2006, at the time of booking in, were analysed. Pre-eclampsia was defined as hypertension and proteinuria. Those with a normal pregnancy were deemed to be controls. Samples were collected for plasma homocysteine, vitamin B12 and folate. MTHFR genotype data was also gathered.

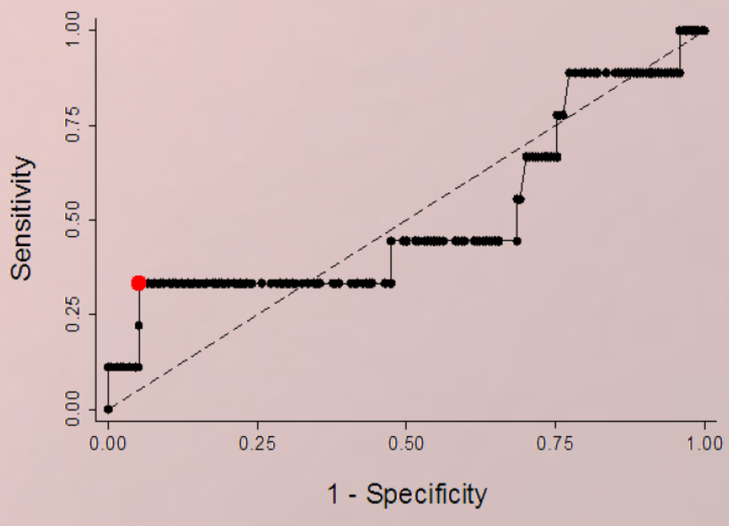
Results

A total of 203 patients were included in the analysis. Of these, 9 developed pre-eclampsia (4.43% [2.3% – 8.3%]). The optimal cut-off point for homocysteine levels was 9.3 µmol/L for maximum specificity and sensitivity (*figure 1*, *table 1*). The area under the ROC curve equals 51%, indicating that the accuracy of homocysteine levels as a diagnostic test for pre-eclampsia is extremely low.

***Table 1* – ROC Analysis**

Statistic	Value (%)	95% CI
Sensitivity	33.33	[7.49 - 70.07]
Specificity	94.85	[90.72 - 97.50]
PPV	23.08	[5.04 - 53.81]
NPV	96.84	[93.25 - 98.83]

***Figure 1* – ROC Curve with Optimal Cut-Off Point**



A Kruskal-Wallis test was performed to assess any underlying relationship between homocysteine level and genotype. The results indicate that there is a statistically significant difference in the mean homocysteine level among the three genotypes at α=5% (*p*=***0.02***).

Figures 2 and *3* show the relationships between homocysteine level and: vitamin B12; and folate. Statistically significant relationships were found between homocysteine levels and three variables: vitamin B12 levels (rho = -0.213, ***p<0.001***); folate levels (rho = -0.386, ***p<0.001***); and smoking (z=-4.47, ***p<0.001***). The Spearman's rank correlation test was used for the first two variables whilst a Wilcoxon-Mann-Whitney test was applied for smoking.

***Figure 2* – Scatter Plot of Relationship Between Homocysteine and Vitamin B12**

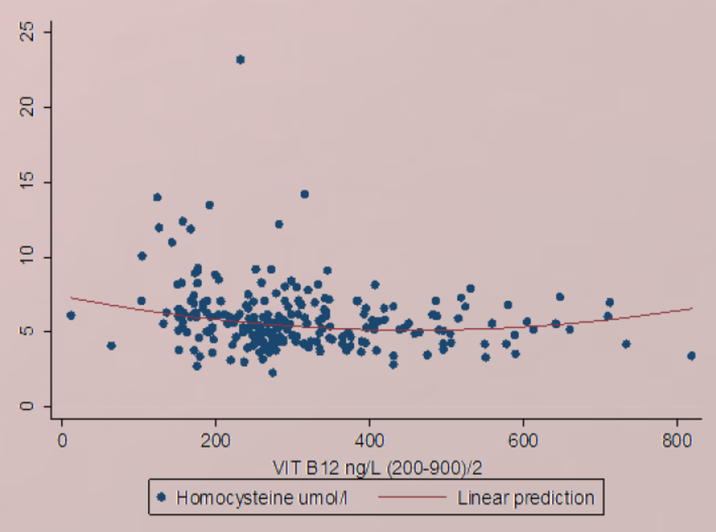


***Figure 3* – Scatter Plot of Relationship Between Homocysteine and Folate**

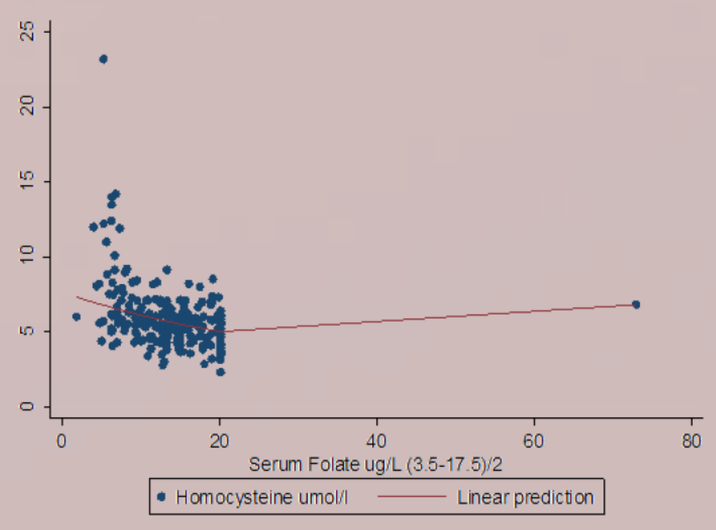


***Table 2* – Univariate Analysis for Variables Investigating Pre-Eclampsia Presence**

Variable	Odds Ratio	95% CI	*P*-value
Smoking (Yes vs. No)	1.04	[0.21 - 5.19]	0.963
Vitamin B12	0.99	[0.99 - 1.01]	0.219
Folate	1.01	[0.93 - 1.11]	0.735
Homocysteine level	1.21	[1.01 - 1.44]	***0.034***

References

1. Walker MC et al. Changes in homocysteine levels during normal pregnancy. *Am J Obstet Gynecol*. 1999;180:660-4.
2. Wald DS. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ*. 2002;325:1202.
3. Lewis SJ. Meta-analysis of MTHFR 677C→ T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ*. 2005;331:1053.

Conclusion

Whilst the odds of pre-eclampsia are significantly raised with a higher homocysteine level, there is no evidence that homocysteine levels can be used as a screening tool. Several factors affect plasma homocysteine levels in pregnancy.

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