

Early Second Trimester hCG of Maternal Serum as Predictor Marker for Pregnancy Induced Hypertension

MUNIRAH M¹, KHALIDAH MB¹, DIAN NASRIANA N¹, HANITA O¹, NOR AZLIN MI²

¹Department of Pathology, ²Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, 56000 Kuala Lumpur, Malaysia

ABSTRAK

Masalah hipertensi akibat kehamilan (PIH) adalah antara punca utama penyakit hipertensi di kalangan wanita hamil. Ia juga merupakan penyebab utama bagi morbiditi dan mortaliti terhadap ibu dan anak. Pertumbuhan serta perkembangan uri yang tidak normal di dalam PIH menyebabkan peningkatan paras hormon hCG di trimester kedua. Jesteru itu, hormon hCG mempunyai peranan di dalam ramalan kejadian PIH. Objektif kajian ini adalah untuk menilai keupayaan hormon hCG di trimester kedua dalam meramal kejadian PIH serta impak obstetrik. Kajian kohort ini melibatkan pengambilan darah bagi analisa paras hormon hCG bagi 34 orang wanita hamil di antara tempoh kehamilan 14-20 minggu. Analisa paras hormone hCG adalah melalui kaedah 'chemiluminescent immunoassay'. Tiga orang wanita hamil (8.8%) menghidapi PIH manakala selebihnya adalah normal. Fungsi hormon hCG di trimester kedua dalam meramal PIH adalah rendah (AUC = 0.398). 'Multiple of median' (MoM) digunakan untuk meningkatkan keupayaan hormon hCG dengan nilai MoM melebihi 2 dianggap sebagai tahap hCG tinggi. Semua kehamilan dengan PIH mempunyai nilai <2 MoM. Bagi kehamilan normal, 29 (93.5%) mempunyai nilai <2 MoM dan 2 (6.5%) dengan nilai >2 MoM ($p>0.655$). Tiada hubungan yang signifikan antara tahap hormon hCG dengan impak kehamilan akibat PIH. Kesimpulannya, nilai hormon hCG pada trimester kedua sebagai penanda ramalan untuk PIH adalah rendah. Limitasi kajian adalah disebabkan kekurangan jumlah kes hipertensi.

Kata kunci: darah tinggi, human chorionic gonadotrophin, kehamilan

Address for correspondence and reprint requests: Munirah Md Mansor. Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91459507 E-mail: dr.muni83@gmail.com

ABSTRACT

Pregnancy induced hypertension (PIH) is commonly encountered in hypertensive disease in pregnancy (HDP) and important cause of feto-maternal morbidity and mortality. Abnormal changes of placenta development in PIH leads to abnormal elevation of second trimester maternal hCG level. Thus, it may have a role in prediction of PIH. The objective of this study was to evaluate the ability of serum hCG levels during early second trimester to predict PIH and obstetric outcome at later gestation. We conducted a cohort study which comprised 34 pregnant women varying from 14–20 weeks of gestation with serum hCG level taken at points of recruitment. Serum hCG was measured by a chemiluminescent immunoassay. Three (8.8%) pregnant women developed late onset PIH while the remainder were normotensive. The diagnostic performance of second trimester hCG in predicting PIH as assessed by receiver operator characteristic curve was poor (AUC = 0.398). Multiple of median (MoM) were used to improve the hCG performance and MoM of >2 MoM were considered as elevated hCG level. All pregnancies with PIH had <2 MoM. In normotensive pregnancy, 29 (93.5%) women had hCG <2 MoM and 2 (6.5%) women had hCG >2 MoM ($p>0.655$). There was no significant association of hCG level and pregnancy outcome. In conclusion, estimation of second trimester hCG is a poor predictive marker for PIH. These findings are limited by the less number of hypertensive cases.

Keywords: hypertension, human chorionic gonadotrophin, pregnancy

INTRODUCTION

Pregnancy induced hypertension (PIH) is among the leading causes of maternal mortality, along with thromboembolism, haemorrhage and non-obstetric injuries. PIH is the hypertension that occurs after 20 weeks gestation and resolves within 12 weeks postpartum. It differs from pre-eclampsia in that there is no proteinuria. Although maternal and neonatal care has improved, PIH still affects 12–15% of all pregnancies (Kaur et al. 2012). The pathogenesis of PIH appears to be reduction of uteroplacental perfusion as a result of

abnormal cytotrophoblast invasion of spiral arterioles. Placental ischaemia is thought to cause widespread activation or dysfunction of the maternal vascular endothelium which results in enhanced formation of endothelin and thromboxane, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide and prostacyclin (Granger et al. 2001). Early recognition of PIH is essential to prevent adverse fetomaternal outcome.

Human chorionic gonadotrophin (hCG) hormone is a sialylated glycoprotein with a mass of 37 kDa, which is secreted by

syncytiotrophoblastic cells of the normal placenta. The hCG molecule is made up of 237 amino acids and consists of two dissimilar α and β subunits. The β -subunit is unique to hCG. During pregnancy, serum hCG concentration increases gradually and reaching a peak at eight to tenth weeks of gestation and progressively declines to a plateau at 18 to 20 weeks of gestation (Yaron et al. 1999). To date, the only known function of hCG is to support corpus luteum during pregnancy by allowing continuous progesterone production and maintenance of the endometrium. hCG also promotes angiogenesis of uterine vasculature by acting on hCG receptors expressed by uterine spiral arteries allowing uterine growth in line with fetal development. hCG is able to regulate placental development by influencing cytotrophoblast differentiation. It also promotes immunosuppression and blockage phagocytosis of invading trophoblast cells (Cole 2012). In view of the role of hCG in angiogenesis and placental development, it may serve as a prediction marker for PIH.

The majority of previous studies investigated hCG in pre-eclampsia and reported that there is an association between high hCG levels and pre-eclampsia especially at second and third trimester (Gurbuz et al. 2004; Yousefnejad et al. 2008; Akbari et al. 2009). Fewer studies have investigated hCG in PIH (Yadav et al. 1997; Sorenson et al. 1993; Feng et al. 2000). These studies were conducted in women at second trimester of more than 20 weeks period of amenorrhoea (POA) or at third trimester of pregnancy

and showed a significant relationship between higher hCG levels and PIH. Only one single study evaluated the ability of hCG taken at early second trimester (13 to 20 weeks POA) to predict PIH and reported that hCG had a sensitivity of 90% and specificity of 97% (Kaur et al. 2012).

Serum total hCG is not an expensive biomarker and its commercial assays are widely available. The ability of hCG in prediction of PIH may assist in clinical judgement and management in antenatal follow up. This may eventually reduce the adverse outcome and help in safe pregnancy. The objective of this study was to determine the clinical usefulness of maternal serum hCG in predicting PIH.

MATERIALS AND METHODS

The cohort study conducted among pregnant women of gestational ages between 14 to 20 weeks POA who presented to the antenatal clinic in the institute's tertiary care medical centre or the maternal and child health clinic in primary care. The study was conducted for the duration of 18 months from January 2014 to December 2015. Inclusion criteria were women with singleton pregnancies, normal blood pressure and no proteinuria (urine protein <300 mg/day). Women with multiple or molar pregnancy, essential hypertension, diabetes mellitus, or history of previous pregnancies involving congenital malformations or Down syndrome were excluded. The study received approval from the Institutional Ethics Board and all

subjects gave their written informed consent.

Venous blood sample was collected on the recruitment day and serum hCG concentration was measured on the same day or within 48 hours (with storage at 4°C) on an automated immunoassay analyser (ARCHITECT, Abbott Diagnostic, USA). The gestational age at time of blood sampling, demographic and medical history were collected at recruitment or retrieved from medical records. Subjects were followed-up until 12 weeks postpartum to observe development of PIH. The subjects were followed-up based on their appointment to the antenatal clinics. Diagnosis of PIH was based on systolic blood pressure became elevated (>140 mmHg) and diastolic pressure increased by more than 25 mmHg above baseline at first trimester without features of pre-eclampsia followed by normalisation of blood pressure 12 weeks postpartum in accordance with the NICE Antenatal Care guidelines. Subjects were also monitored for other hypertensive outcomes to the mother (pre-eclampsia, eclampsia, HELLP syndrome) or adverse outcomes for the fetus (small for gestational age, oligohydramnios or intrauterine death) as defined in the NICE guidelines.

The clinical and laboratory data were stored and analysed by the Statistical Package for Social Sciences (SPSS) software version 22.0. All quantitative variables were expressed as mean \pm 1 standard deviation (\pm SD) for normally distributed data or median (range) for data without normal distribution. Serum hCG levels in subjects with

and without PIH were compared using Mann-Whitney U test; ethnicity and parity were compared using Chi squared test. Pearson or Spearman correlation coefficients were calculated to estimate linear correlation between continuous variables as appropriate. Multiples of the median (MoM) was calculated by dividing the hCG result in each sample by the median hCG at the corresponding gestational age. A cut-off value of more than 2 MoM was used as it has significant relation with PIH. The ability of hCG at second trimester to predict PIH was determined by receiver operating characteristic (ROC) curve analysis and calculating sensitivity, specificity, positive predictive value and negative predictive value. In all analysis, $p < 0.05$ (95% confidence interval) was considered to be significant.

RESULTS

A total of 34 pregnant women were recruited with a mean (\pm SD) gestational age of 18 ± 2 weeks. The mean (\pm SD) maternal age was 30 ± 2 years old. The pregnant women are of Malay (26) and Chinese (8). In this cohort, three women developed PIH (8.8%), whereas all of the other women remained normotensive throughout pregnancy. All women with PIH were Malays. Two women had preterm delivery and the remaining had full term delivery. Of those women who delivered at full term gestation, 16.1% had gestational diabetes mellitus (GDM). None of the GDM patients had PIH. There was no critical difference found in race, maternal age, gestational age, or parity

Table 1: General characteristics of study population

	All subjects	Pregnancy without hypertension	PIH	p value
Number of patients (%)	34	31 (91.2)	3 (8.8)	
Race				
Malay	26	23	3	0.434 ^a
Chinese	8	8	0	
Age, years (mean±SD)	30±4	32±6	30±4	0.603 ^b
Gestation, weeks (mean±SD)	18±2	18±2	18±2	0.969 ^b
Parity (%)				
Primigravida	14	13 (92.9)	1 (7.1)	0.773 ^a
Multigravida	20	18 (90.0)	2 (10.0)	

^aby Chi-squared, ^bby Student t-test, statistical significant at $p < 0.05$

between PIH and non-PIH pregnancies but the occurrence of PIH was higher among multigravida (Table 1).

The median (range) serum hCG level in women with and without PIH was 24225 mIU/ml (17173-42720) and 28776 mIU/ml (9316-65148), respectively (Table 2). There was no significant difference between the two groups, $p=1.00$. All three women with PIH had hCG levels that were less than 2 MoM whereas two normotensive pregnant women had hCG greater than 2 MoM. However, this difference was not significant ($p=0.655$). The serum hCG level of those in PIH group were

below of 50000.00 mIU/ml compared to normotensive group (Figure 1). There was no association of increasing serum hCG level with diagnosis of PIH.

ROC curve analysis showed that the diagnostic performance of second trimester hCG level to predict PIH was poor with an area under the curve (AUC) of 0.398 (95% CI: 0.111-0.685), $p=0.564$ (Figure 2 and Table 3).

All PIH cases were diagnosed as mild, late onset PIH and required induction of labour at term for delivery of the baby. All babies were healthy with no complications. There were no correlation of maternal serum hCG

Table 2: Maternal serum hCG in normotensive and PIH group

	Statistic	Normotensive (n=31)	PIH (n=3)	p value
	Median (range)	28776 (9316 - 65148)	24225 (17173 - 42720)	1.000 ^a
Serum hCG (mIU/ml)	MoM			0.655 ^a
	≤ 2MoM	29	3	
	> 2MoM	2	0	

^aby Mann-Whitney U test, statistical significant $p < 0.05$.

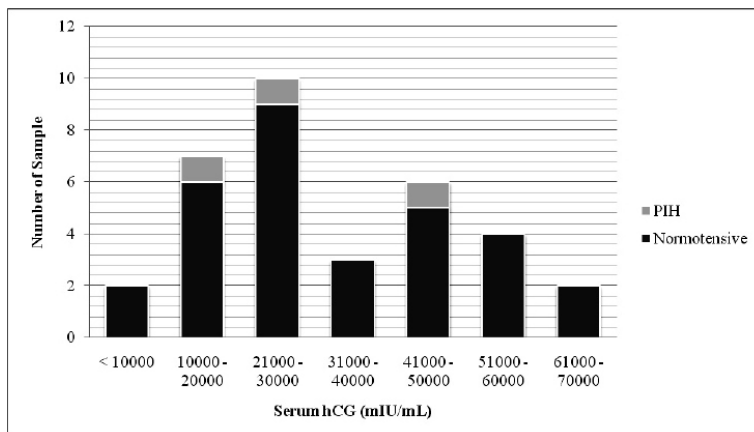


Figure 1: Distribution of second trimester maternal serum hCG

level with regard to severity, onset and fetal outcome in those women with PIH.

DISCUSSION

According to World Health Organization (WHO) data, pregnancy induced hypertension (PIH) is one of the important causes of maternal,

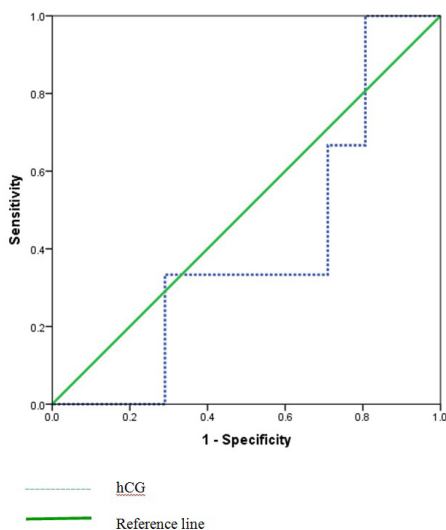


Figure 2: Receiving operator characteristic (ROC) curve of maternal serum hCG as predictor marker for PIH.

fetal and neonatal mortality and morbidity. The condition complicates about 6 to 10% of pregnancies. In the present study, 8.8% of the pregnancies developed PIH which is consistent with WHO data.

In a retrospective study in India, PIH was described as the third cause of maternal death (Kintiraki et al. 2015). In the Henan province of China, PIH was the second factor of maternal death (You et al. 2012). While in Malaysia, it was the third cause of maternal death (Kaur et al. 2011). Pregnant women with PIH are at greater risk of developing *abruptio placentae*, cerebrovascular events, organ failure and disseminated intravascular coagulation. Babies who were born to these mothers are at greater risk of intrauterine growth retardation, prematurity and intrauterine death.

There are various complications of PIH that can affect pregnant women diagnosed with the disease. The complications would increase severity of the illness especially for those pregnant women who did not have

Table 3: ROC Analysis of serum hCG

Test	AUC	p value	95% Confidence interval	
			Lower bound	Upper bound
hCG	0.398	0.564	0.111	0.6585 ^a

proper follow-up of the pregnancy. Pregnant women with PIH were at high risk of adverse pregnancy outcomes than those without PIH and delay in seeking care is one of the major challenges in management of PIH. Thus, this will cause problem in obstetrical management and result in poor outcome of pregnancy (Muti et al. 2015).

Abnormal hCG levels are known to be associated with certain pregnancy complications such as multiple pregnancy, gestational trophoblastic disease, and chromosomal abnormalities of the fetuses (Keay et al. 2004). Unexplained elevation of hCG in second trimester appears to be correlated with higher frequency of gestational hypertension with proteinuria (pre-eclampsia) with or without adverse features, preterm labour, stillbirth, and intrauterine growth retardation (Gagnon et al. 2008).

In this study, we evaluated the efficacy of second trimester hCG level as a predictive biomarker for PIH. The median hCG level in normotensive pregnancies was higher than the pregnancies with PIH, however, the difference was not statistically significant. This finding is in contrast to previous studies which mostly report higher hCG in hypertensive pregnancy or pre-eclampsia compared

to normotensive pregnancies (Dubey et al. 2013; Yadav et al. 2014).

Sensitivity, specificity of hCG to predict PIH was assessed by ROC curve. The AUC was 0.398 which indicates poor performance. From the ROC, serum hCG has low sensitivity (67-100%), specificity (19-23%), and extreme low of PPV and NPV. Therefore in this study, there was no significant value of maternal serum hCG taken at second trimester as a tool for prediction of PIH.

Since actual values of hCG were not good indicators of PIH, we evaluated whether using MoM might improve the performance by taking into account gestational age. The most common cut-off values used for MoM in mid-trimester are between 2 and 2.5 MoM as it has significant impact on the pregnancy outcomes (Gagnon et al. 2008; Androutsopoulos et al. 2012). Currently, there is no established local data on median hCG levels at different gestational ages. For this study, the MoM value was derived from the calculation on the available current data that has been explained in the methodology. From this study, all patients with PIH had hCG less than 2 MoM and majority of normotensive pregnancies had hCG less than 2 MoM. Other previous studies found that there was no association between elevation of maternal serum hCG

and pre-eclampsia at multiple cut-off points of 1.5, 2.0, 2.5, and 3.0 (Stamilio et al. 2000). In contrast to a recent study, they found a highly significant association between PIH and hCG level more than 2 MoM (Kaur et al. 2012).

In this study, two cases of normotensive pregnancies had hCG values of more than 2 MoM. Both women were less than 30 years old and primigravida. The serum hCG levels were taken at gestational age of 19 weeks. One of the cases had an antenatal problem of mild polyhydramnios. However, there was no exact cause of polyhydramnios in the patient after proper investigations were done in the health centre. Her baby was safely delivered and healthy. The second case had no significant antenatal or postnatal problems. According to a study on elevation of hCG in second trimester with regard to pregnancy outcomes, there is no relationship of elevated hCG level (> 2 MoM) with polyhydramnios incidence (Bojana et al. 2004).

All PIH cases were diagnosed as late onset PIH with mild severity (non proteinuric) and all had good outcome of the fetus. According to Kintiraki et al. (2015), complications are more frequently encounter in early onset PIH (gestational less than 32 weeks) compared with late onset. Therefore, the cases of PIH in this study were consistent with the previous finding. Furthermore, most reports indicate that complications of PIH mostly occur in the mother.

In this study, the maternal age, gestational age, parity and race had

no association with incidence of PIH. In other recent study reported similar finding as no association between maternal age, parity or race with the occurrence of PIH but they also found out that the primigravida had high occurrence of PIH compared to multipara (Kaur et al. 2012). In contrast, in the present study, the occurrence of PIH was higher in multigravida compared to primigravida pregnancies but there was no significant association pertaining to development of PIH. The mean serum hCG in PIH of primigravida was 42720 (± 0.0) mIU/ml and in multigravida was 20698 (4986) mIU/ml. The serum hCG level in the multigravida case with PIH was taken at 20th week of gestation with the level below than 2 MoM.

In the present study, we included pregnancies that developed into gestational diabetes mellitus (GDM) during the follow-up. GDM was associated with severe pre-eclampsia, mild pre-eclampsia, and gestational hypertension and that women with GDM had 1.5-fold overall risk of developing a hypertensive disorder of pregnancy (Bryson et al. 2003). The incidence of PIH was high among GDM pregnant women who had less prenatal care (Muti et al. 2015). However, none of the women with GDM in this study developed PIH. Based on recent report of epidemiological data, there is no clear association of GDM and PIH except insulin resistance (Perveen et al. 2015).

This study was limited by the less number of PIH cases although it was consistent with the reported prevalence rates. The study was

conducted in single centre which may have contributed to the bias in the data.

CONCLUSION

In conclusion, maternal serum hCG taken at second trimester to predict PIH has low sensitivity, specificity, PPV and NPV. However, since this study was underpowered, we cannot reject the hypothesis that hCG may have some role in predicting PIH. There was no association between the level of serum hCG and severity of PIH and obstetric outcome. Further studies are required and as well as the establishment of MoM values in the local population.

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