Volume-6, Issue-2, February - 2017 • ISSN No 2277 - 8160 IF : 3.62 | IC Value 80.26

Original Research Paper Gynaecology

Human Chorionic Gonadotropin (Hcg)- Levels In Pre-Eclampsia And Hyperemesis

Kalpana Thalava	Associate Professor, Department of obstetrics and Gynecology, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry.
Manmatharaj	Assistant Professor of General Medicine, Sri Lakshmi Naryana Institute of Medical Sciences, Puducherry
E.Prabhakar Reddy	Professor, Department of Biochemistry, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry
A.Vaithialingam	Professor, Department of Orthopedics, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry.

ABSTRACT Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality worldwide. A predictor of pre-eclampsia would enable intervention, close surveillance and timely delivery, and thereby reduce the negative consequences of the disorder. The overall aim of this work was to study potential predictors of pre-eclampsia by Biochemically by hcg. In the group of women who developed pre-eclampsia the levels of hcg were significantly lower in gestational weeks and second trimesters compared to women with a normal healthy pregnancy and also in first trimester. ($p<0.05$). As hCG levels may be both a cause and an effect of placentation, time of onset of hyperemesis gravidarum may be a clinical marker of risks of preeclampsia and other abnormal placentation disorders. In very early pregnancy,high hCG levels may favour normal pregnancy development, while later in pregnancy, abnormal placentation may cause high hCG levels and thereby hyperemesis gravidarum.

KEYWORDS : Pre-Eclampsia, Hyperemesis Gravidarum, Early Pregnancy.

INTRODUCTION

Nausea and vomiting are common and usually benign symptoms of primarily the first trimester of pregnancy. The onset of nausea correlates with the level of human chorionic gonadotropin (hCG), which typically rises within 4 weeks after the last menstrual period, peaking at approximately 9 weeks of gestation [1]. Sixty percent of nausea cases resolve by the end of the first trimester and 91% by 20 weeks of gestation [1]. Hyperemesis gravidarum is at the severe end of the nausea spectrum and according to The International Statistical Classification of Disease and Related Health Problems (ICD-9), is defined as 'persistent and excessive vomiting starting before the end of the 22nd week of gestation'. Hyperemesis gravidarum is clinically classified as mild or severe, depending on associated metabolic disturbances such as carbohydrate depletion, dehydration and electrolyte imbalance. Its incidence is estimated at 0.3 to 1.5% of all live births but is unevenly distributed on a global level [2–6]. Asian women, for instance are more likely to suffer from hyperemesis than Caucasian women [3, 5]. Hyperemesis greatly affects maternal well-being and quality of life [7, 8] and is among the most common reasons for pregnancy-associated hospitalization [6-10].

Pre-eclampsia, placental abruption, stillbirth and small for gestational age (SGA) birth are associated with abnormal placentation [12-14].The trophoblast migration into the maternal deciduas and adjacent spiral arteries, which starts in early pregnancy and continues until about the 20th week of gestation, is restricted in these disorders[15]. Human chorionic gonadotrophin (hCG) is probably an important regulator of this complex process[16]. There are several variants of hCG. Hyperglycosylated hCG (hCG-H), which is the principal variant of hCG in very early pregnancy, is supposed to be especially important for the stimulation of trophoblast migration[17]. In the second trimester, hCG-H levels dwindle to less than 1% of total hCG[17]. Elevated hCG levels in the second trimester could be a result of an insufficient first-trimester trophoblast migration into the spiral arteries, with a subsequent placental hypoxia that stimulates the secretion of other variants of hCG[16]. Low first-trimester and increased second-trimester hCG levels are associated with later development of pre-eclampsia and SGA[18-19].

Another pregnancy complication associated with high hCG levels is hyperemesis gravidarum[20], a severe form of nausea and vomiting. Hyperemesis gravidarum occurs in 0.5–3% of pregnancies and is the most common cause of hospitalisation in the first half of the pregnancy[21]. In a recent meta-analysis[22], an increased risk of SGA was reported in women with hyperemesis gravidarum, but other placental dysfunction disorders were not evaluated. We have found only one study of hyperemesis gravidarum and other placental dysfunction disorders, which supports a weak association between hyperemesis gravidarum and pre-eclampsia risk[23].

As hCG levels may be both a cause and an effect of placentation, the time of onset of hyperemesis gravidarum may influence the risks of abnormal placentation disorders. In very early pregnancy, high hCG levels may favour normal pregnancy development, whereas, later in pregnancy, abnormal placentation may cause high hCG levels.

MATERIAL AND METHODS

The study included 30 women with an uncomplicated pregnancy (controls) and 30 women who developed preeclampsia (cases) were enrolled in gestational week and Only women with singleton pregnancies were recruited. Only women with singleton pregnancies were recruited. Women with a concurrent diagnosis such as chronic hypertension, episodes of high blood pressure before pregnancy, persistently elevated blood pressure, upper urinary tract infection, pre-existing renal disease, diabetes mellitus, and drug abuse were not included. Plasma samples were collected in lithium/heparin containing tubes at gestational weeks, and total study was conducted in SLIMS, Pondicherry. Maternal blood was collected in non-heparinized tubes. The blood samples were on average collected at gestational week 14. Patient characteristics including demographics, smoking status, and obstetric and medical history were obtained from women at the first hospital visit and entered into a foetal medicine unit database. Pre-eclampsia was defined as two recordings of blood pressure of 140/90 mmHg or greater at least 4 hours apart and proteinuria of 300 mg or more within 24 hours, or two readings of at least 2 on dipstick analysis of

urine if a 24-hour collection was not available, and developed after 20 weeks of gestation.

Statistics:
All statistical analysis was performed by the SPSS 15.0 for Windows software package (SPPS, Chicago, IL). Among the background variables a chisquare test was used for proportions. For comparisons of median values a Mann–Whitney U test was used for independent samples and for mean values students t-test was used. P-values ≤0.05 were considered as statistically significant.

RESULTS
A possible association between hyperemesis gravidarum and pre-eclampsia, as well as other placental dysfunctional disorders, was investigated. Hyperemesis gravidarum may be caused by high levels of human chorionic gonadotrophin (hCG) and increased levels of hCG in the second trimester is associated with later development of pre-eclampsia. The results indicated that the mean hcg levels decreased as the pregnancy proceeded in all women, irrespective of whether they developed preeclampsia or not. However, in the group of women who developed pre-eclampsia the levels of hcg were significantly lower in gestational weeks and second trimesters compared to women with a normal healthy pregnancy and also in first trimester. ($p<0.05$). The high levels of hCG in the second trimester could be a compensatory mechanism to an insufficient early trophoblast migration and invasion of the spiral arteries, which could be due to a low level of H-hCG, the variant of hCG that stimulates invasion in very early pregnancy. Thus, abnormal placentation may cause high levels of hCG in the second trimester, which then causes hyperemesis gravidarum with a late onset.

DISCUSSION
Hyperemesis gravidarum is, according to our results it is associated with increased risks of pre-eclampsia, placental abruption, and SGA birth. These risks were especially associated with hospitalization due to hyperemesis gravidarum in the second trimester. As pre-eclampsia, placental abruption and SGA birth are associated with abnormal placentatio[24-25].

Low first trimester βhCG, which is a hyperglycosylated variant of the β-subunit of hCG, and increased second trimester hCG are associated with adverse obstetrical outcome.Elevated hCG levels in the second trimester could be due to a reduced production of (H-hCG) early in pregnancy, which results in an insufficient trophoblast migration into the spiral arteries, with a subsequent placental hypoxia that stimulates secretion of the pro-angiogenic hCG as a compensatory mechanism. As hCG levels may be both a cause and an effect of placentation, time of onset of hyperemesis gravidarum may be a clinical marker of risks of preeclampsia and other abnormal placentation disorders. In very early pregnancy, high hCG levels may favour normal pregnancy development, while later in pregnancy, abnormal placentation may cause high hCG levels and thereby hyperemesis gravidarum[25].

Our findings indicate an association between abnormal placentation and hyperemesis gravidarum manifested in the second trimester.The finding of an increased risk of pre-eclampsia for women with hyperemesis gravidarum is in agreement with one former study. Our study has increased understanding about the association between the disorders,since we separated preterm from term pre-eclampsia. The discovery of a stronger association between hyperemesis gravidarum and preterm rather than term pre-eclampsia suggests that hyperemesis gravidarum is associated with abnormal placentation. In addition, after stratifying hyperemesis gravidarum by hospitalization in the first or the second trimester, we could clearly show that it is hyperemesis gravidarum in the second trimester that is associated with preterm pre-eclampsia risk and accordingly with abnormal placentation.

Earlier studies report an association between high levels of total hCG in the second trimester and risk of pre-eclampsia and SGA birth. Our findings are in agreement with these studies, since hyperemesis gravidarum is associated with high levels of hCG. The high levels of hCG in the second trimester could be a compensatory mechanism to an insufficient early trophoblast migration and invasion of the spiral arteries, which could be due to a low level of H-hCG, the variant of hCG that stimulates invasion in very early pregnancy. Thus, abnormal placentation may cause high levels of hCG in the second trimester, which then causes hyperemesis gravidarum with a late onset.

There are also other possible explanations to our findings. Hyperemesis gravidarum is a classical example of an interaction of biological and psychosocial factors [26]. There are associations with both high thyroxin and estradiol levels [27]. HCG is structurally similar to thyroid-stimulating hormone and an increased production of thyroxin is associated with hyperemesis gravidarum. Women with second trimester hyperemesis might have a prolonged or delayed stimulation of thyroxin, compared to women with first trimester hyperemesis. This might affect placentation, since former studies have shown an association between hyperthyreosis and placental dysfunction disorders [28]. Pre-eclampsia is mostly associated with low estradiol levels, and we therefore doubt that estradiol is a link between these disorders [29].
An epidemiological study cannot explain why hyperemesis gravidarum with a late onset could be associated with placental dysfunction disorders but hyperemesis gravidarum in the second trimester may be a clinical risk predictor to consider when predicting the risk of pre-eclampsia and other disorders associated with abnormal placentation.

Prediction of pre-eclampsia in our study and future studies:
Prediction of pre-eclampsia, which would make possible early detection and give the opportunity to intervene by correcting the pathophysiological changes, demands increased knowledge about the process that leads to the development of pre-eclampsia. Through studies of potential predictors we have learned more about the pathophysiology of pre-eclampsia.

A reliable predictive test would help us to individualize the level of surveillance during pregnancy. It is, though, important to remember that there are a number of, mainly low-income, countries around the world, where the majority of the maternal and perinatal complications related to pre-eclampsia appear, that would benefit from just a better and wellfunctioning maternal care. However, an easy and sensitive predictive test would help to save lives, even in poorer countries, since this could help the midwife to recommend the woman to come for more frequent controls and maybe also to be delivered at a hospital. In high-income countries a predictor of pre-eclampsia could be used to prevent or postpone the disorder by prophylactic treatment.

To be able to intervene with defects in implantation and placentation that might lead to increased risk of pre-eclampsia, the ultimate predictor should be able to identify women with an increased risk as early as in the first trimester. Since pre-eclampsia is a very heterogenous disorder, a predictive test should be constructed by using different markers of importance that reflect different aspects of the pathogenesis. Potential components of such a combination could be anamnestic risk factors, angiogenic, inflammatory and other biochemical factors, uterine artery Doppler and MAP. We postulate that the biochemical markers HRG and the Ang-1/Ang-2 ratio that we have studied would be interesting to study in a combined model for prediction of the disease. Hyperemesis gravidarum in the second trimester as a clinical risk predictor could also be considered, as demonstrated in our epidemiological study.

It has been discussed which category of patients a test should be capable of identifying and, since women with early-onset pre-eclampsia often have worse symptoms and a more severe disease, it might be postulated that this category would be of interest to focus

on. This would make it possible to offer prophylactic treatment and increased surveillance, which presumably should be more cost effective with a reduced maternal and foetal morbidity and mortality as a consequence. Potentially, it should be possible to construct a predictive test for pre-eclampsia of a placental origin by including biochemical factors that reflect different steps of inadequate implantation and/or placentation in combination with uterine artery Doppler. Preeclampsia with a maternal origin could possibly be identified with a relatively high sensitivity and specificity by a combination of known risk factors and MAP.

The combination of biophysical methods and several other factors makes the tests more expensive and several of the tests use technologies that are not widely available. In low-income countries there is a need for more studies of potential predictors that use simple and inexpensive technology, as well as non-invasive screening methods such as dipstick tests of urine. Some studies have investigated the potential to use urinary analyses for prediction of preeclampsia[30-32] although the results have varied.

The theory that hyperemesis gravidarum in the second trimester is induced by high levels of hCG, which is increased as a compensatory mechanism to low H-hCG early in pregnancy, has aroused interest in H-Hcg as another potential predictor of pre-eclampsia. In contrast to hCG produced by syncytial trophoblast, extravillous trophoblast secretes H-hCG that has been demonstrated to stimulate invasion. H-hCG levels, in serum and in urine, seem to be a reliable test to diagnose pregnancies after in vitro fertilization treatment as early as six days after embryo transfer, and, in addition, to separate whether a pregnancy is a clinical pregnancy or a biochemical pregnancy[33]. As a predictor of pre-eclampsia, lower levels of H-hCG in the urine have been demonstrated in the second trimester for women who later developed pre-eclampsia compared with normal pregnancies[30]. Since H-hCG is of importance from the very beginning of the implantation and is the most common form of hCG during the first weeks afterward, it is an interesting potential predictor. An advantage is the possibility for detecting H-hCG in urine in very early pregnancy. Further studies of the ability for H-hCG to predict pre-eclampsia early in pregnancy would be of interest.

In the search for new potential predictors of pre-eclampsia, GWAS offers,new possibilities to screen the human genome and further evaluate different gene expressions. The result of genetic studies could either be a specific SNP as a predictor of pre-eclampsia or a protein or molecule that the different gene expressions are coding for.

For screening tests in general a premium is placed on a low rate of false positive results but for pre-eclampsia a false negative result could pose a high risk and therefore a somewhat lower specificity than usual should be accepted. Suggested cut-off values out of the ROC curves in study II and III were chosen to prioritize a high sensitivity, even if relatively low specificity may cause increased concern and anxiety for the women.

With a low specificity, several women who would never have developed pre-eclampsia would be offered prophylactic treatments and increased surveillance. This fact increases the need for the treatment to be safe and without any side-effects. The level of surveillance also has to be acceptable for the women. The possibilities of prophylactic treatment are limited, since no specific treatment is provided, but for a high risk group antiplatelet drugs, i.e. low dose aspirin, seems to have a relative good effect in preventing or postponing the disorder, at least if the treatment is started early in pregnancy[13]. It is also important to evaluate other different possible prophylactic treatments, where a substance such as heparin might be of interest. Intervention as early and as specific as possible in the development of pre-eclampsia is recommended. The ultimate would be to start treatment before the trophoblast invasion of the myometrium happens. It might also, in the future, be possible to start a potential prophylactic treatment even before the pregnancy begins, based on genetic testing and counselling. The possibility of over-expressing angiogenic factors in viral vectors for injection in the myometrial wall to optimize the angiogenic status has also been discussed but there are no such studies on-going on humans yet.

At present there are several predictive tests that do reach rather high sensitivity and specificity. The next step is to evaluate whether these tests,in combination with prophylactic treatment and/or increased surveillance, reduce the incidence or postpone diagnosis and improve the maternal and neonatal outcome. To perform these studies a multicenter approach with randomized controlled trials has to be made to achieve a decent number of patients at risk of pre-eclampsia. pre-eclampsia might be possible to predict". To investigate whether there are any clinical benefits related to prediction, further studies are needed.

CONCLUSION

This might also occur with hyperemesis and, therefore, further research on the placenta is warranted; especially since there is evidence that compensatory growth of the placenta is associated with cardiovascular problems in later life. Hyperemesis gravidarum is an invalidating disease in early pregnancy, associated with hospitalizations, use of medication and a poorer quality of life. However, our findings do indicate no relevant impact of hyperemesis gravidarum on placental dysfunction disorders. In this study has demonstrated associations between hyperemesis gravidarum diagnosed in the second trimester and placental dysfunction disorders, i.e. preterm pre-eclampsia, placental abruption.

The ultimate predictor of preeclampsia should presumably identify women with an increased risk of the disorder as early as in the first trimester. The test should also be simple,rapid, non-invasive, inexpensive and the technology widely available. Furthermore it should be valid, reliable and reproducible with a high positive and a low negative likelihood ratio.

REFERENCES

1. Niebyl JR. Nausea and vomiting in pregnancy. N Engl J Med. 2010;363:1544–1550.
2. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta-analysis. J Popul Ther Clin Pharmacol. 2013;20(2):e171–83.
3. Vikanes A, Grjibovski AM, Vangen S, Magnus P. Variations in prevalence of hyperemesis gravidarum by country of birth: a study of 900,074 pregnancies in Norway, 1967–2005. Scand J Public Health. 2008;36(2):135–42.
4. Jordan V, MacDonald J, Crichton S, Stone P, Ford H. The incidence of hyperemesis gravidarum is increased among Pacific Islanders living in Wellington. N Z Med J. 1995;108(1006):342–344.
5. Matsuo K, Ushioda N, Nagamatsu M, Kimura T. Hyperemesis gravidarum in Eastern Asian population. Gynecol Obstet Invest. 2007;64(4):213–6.
6. Verberg MFG, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11(5):527–39.
7. McCarthy FP, Khashan AS, North RA, et al. A prospective cohort study investigating associations between hyperemesis gravidarum and cognitive, behavioural and emotional well-being in pregnancy. PLoS One. 2011;6(11):e27678.
8. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol. 2010;31(1):10–20.
9. Bacak SJ, Callaghan WM, Dietz PM, Crouse C. Pregnancy-associated hospitalizations in the United States, 1999–2000. Am J Obstet Gynecol. 2005;192(2):592–7.
10. Gazmararian JA, Petersen R, Jamieson DJ, et al. Hospitalizations during pregnancy among managed care enrollees. Obstet Gynecol. 2002;100(1):94–100.
11. Trogstad LIS, Stoltenberg C, Magnus P, Skjærven R, Irgens LM. Recurrence risk in hyperemesis gravidarum. BJOG. 2005;112(12):1641–5.
12. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod. 2003;69:1–7.
13. Dommisse J, Tiltman AJ. Placental bed biopsies in placental abruption. Br J Obstet Gynaecol. 1992;99:651–4.
14. Smith GC, Fretts RC. Stillbirth. Lancet. 2007;370:1715–25.
15. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204:193–201.
16. Chen JZ, Sheehan PM, Brennecke SP, Keogh RJ. Vessel remodelling, pregnancy hormones and extravillous trophoblast function. Mol Cell Endocrinol. 2012; 349: 138–44. [PubMed]
17. Cole LA. Hyperglycosylated hCG, a review. Placenta. 2010;31:653–64. [PubMed]
18. Canini S, Prefumo F, Pastorino D, Crocetti L, Afflitto CG, Venturini PL, et al. Association between birth weight and first-trimester free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril. 2008;89:174–8. [PubMed]
19. Lepage N, Chitayat D, Kingdom J, Huang T. Association between second-trimester isolated high maternal serum human chorionic gonadotropin levels and obstetric complications in singleton and twin pregnancies. Am J Obstet Gynecol. 2003;188:1354–9. [PubMed]

20. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11:527–39. [PubMed]
21. Roseboom TJ, Ravelli AC, van der Post JA, Painter RC. Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 2011;156:56–9.
22. Veenendaal MV, Van Abeelen AF, Painter RC, van derPostJA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG. 2011;118:1302–13.
23. Zhang J, Cai WW. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. Epidemiology. 1991;2:454–7.
24. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod 2003;69(1):1-7.
25. Dommisse J, Tiltman AJ. Placental bed biopsies in placental abruption. Br J Obstet Gynaecol 1992;99(8):651-4.
26. Lub-Moss MM, Eurelings-Bontekoe EH. Clinical experience with patients suffering from hyperemesis gravidarum (severe nausea and vomiting during pregnancy): thoughts about subtyping of patients, treatment and counseling models. Patient Educ Couns 1997;31(1):65-75.
27. Tamay AG, Kuscu NK. Hyperemesis gravidarum: current aspect. J Obstet Gynaecol 2011;31(8):708-12.
28. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstet Gynecol 1994;84(6):946-9.
29. Shenoy V, Kanasaki K, Kalluri R. Pre-eclampsia: connecting angiogenic and metabolic pathways. Trends Endocrinol Metab 2010;21(9):529-36.
30. Bahado-Singh RO, Oz AU, Kingston JM, Shahabi S, Hsu CD, Cole L. The role of hyperglycosylated hCG in trophoblast invasion and the prediction of subsequent pre-eclampsia. Prenat Diagn 2002;22(6):478-81.
31. Lindqvist P, Grennert L, Marsal K. Epidermal growth factor in maternal urine-- a predictor of intrauterine growth restriction? Early Hum Dev 1999;56 (2-3):143-50.
32. Savvidou MD, Akolekar R, Zaragoza E, Poon LC, Nicolaides KH. First trimester urinary placental growth factor and development of pre-eclampsia. BJOG 2009;116(5):643-7.66
33. Strom CM, Bonilla-Guererro R, Zhang K, Doody KJ, Tourgeman D, Alvero R, et al. The sensitivity and specificity of hyperglycosylated hCG (hhCG) levels to reliably diagnose clinical IVF pregnancies at 6 days following embryo transfer. J Assist Reprod Genet 2012;29(7):609-14.