

Hypoxia-inducible factor-1 α as a predictive marker in pre-eclampsia

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Abstract. The aim of this study was to determine whether or not the increased levels of hypoxia-inducible factor-1 α (HIF-1 α) could be used to demonstrate failed placentation in pre-eclamptic mothers. Twenty pregnant females with (pre-eclampsia group) or without pre-eclampsia (control group) were included in the present study. Antenatal and post-delivery HIF-1 α transcription factor levels were measured. A significant increase was observed in the HIF-1 α levels in the pre- and post-natal pre-eclampsia mothers. The findings suggest that the levels of HIF-1 α in the blood of mothers with pre-eclampsia decrease after delivery of the placenta. The results confirm that there is increased HIF-1 α in pre-eclampsia and a steady increase in the levels of HIF-1 α could be commensurate with the possibility of a patient developing pre-eclampsia at a later trimester.

Introduction

Pre-eclampsia is a pregnancy-specific disorder of variable severity displaying a characteristic presentation with well-defined diagnostic criteria in place solely based on physical signs, such as hypertension and proteinuria, although some aspects of its pathophysiology have yet to be ascertained and described. The placenta being placed at a strategic location successfully interfaces the maternal and foetal circulation during pregnancy and exits its location immediately after delivery when it has fulfilled its function. As a result of a physiological process termed 'pseudovasculogenesis', the spiral arterioles increase in diameter and reduce in muscula-

ture thus increasing the amount of blood supplied to the foetus, a process that is absent in pre-eclampsia.

Pre-eclampsia has been a major cause of maternal and foetal mortality worldwide despite its predictable presentation. The need for a predictive marker for pre-eclampsia is understated but has been a subject for discussion throughout the scientific community. The search for a consistently expressed and easily measurable 'substance' that can act as a marker for pre-eclampsia is still underway and therefore defines the purpose of this study.

Hypoxia-inducible factor-1 α (HIF-1 α) is a transcription factor transiently expressed as a protein (1,2), also binding to hypoxia-response elements (HREs) in the promoters of several genes involved in the adaptation to an environment of hypoxia. Its consistent presence in hypoxic milieus renders it a notable candidate for pre-eclampsia-related research. Previous studies have demonstrated the presence of HIF-1 α in pre-eclamptic placentas (1,2), but whether escalating levels of the protein parallel aberrant pseudovasculogenesis has yet to be evaluated. This study aimed to determine whether or not the increased levels of HIF-1 α can be used to demonstrate failed placentation in pre-eclamptic mothers, thereby establishing its credibility as a blood marker for pre-eclampsia.

Materials and methods

A case-control pilot study involving two groups of ten mothers with and without pre-eclampsia, respectively, was initiated by the authors from the International Medical University, Kuala Lumpur, Malaysia, in collaboration with the co-authors from Hospital Ampang, Kuala Lumpur, Malaysia. Consenting mothers (age, <45 years), with newly diagnosed pre-eclampsia and devoid of co-morbidities such as diabetes mellitus and essential hypertension, formed the study group, while consenting mothers within the same age group with normal pregnancies constituted the control group. The study was approved by the ethics committee of International Medical University, Kuala Lumpur, Malaysia. HIF-1 α transcription factor levels were measured in venous blood drawn antenatally at diagnosis, and thereafter immediately after delivery of the placenta by enzyme-linked immunosorbent assay (ELISA). Additional characteristics such as placental weight and urinary protein levels were included. Data are expressed

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Abbreviations: HIF, hypoxia-inducible factor; HRE, hypoxia-response elements; ELISA, enzyme-linked immunosorbent assay

Key words: pre-eclampsia, hypertension, hypoxia-inducible factor, pregnancy

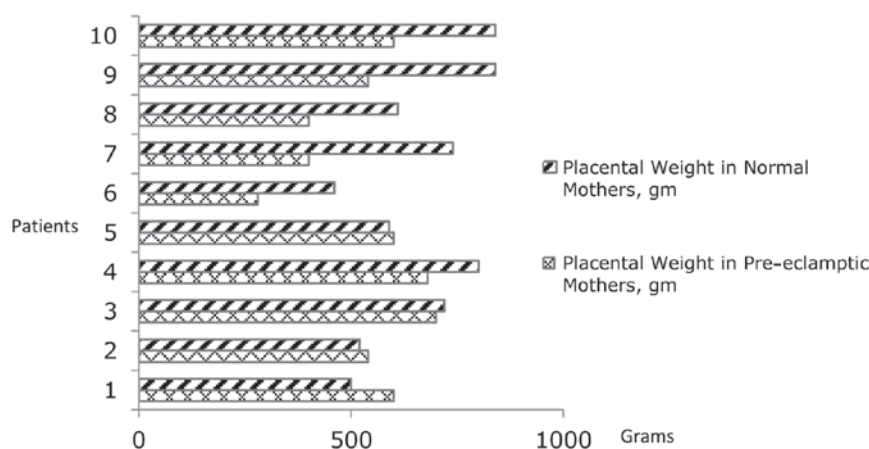


Figure 1. The placental weights of normal mothers and mothers with pre-eclampsia.

as the means \pm standard error of the mean (SEM). Data were analyzed using analysis of variance coupled with a post hoc Tukey's test for multiple pairwise comparisons. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The age of the pre-eclamptic mothers included in the study ranged from 20 to 35 years, while that of the normal mothers ranged from 23 to 35 years.

The placental weights in normal mothers were greater when compared to the pre-eclamptic mothers (Fig. 1). Twenty-four-hour urine protein levels in pre-eclampsia patients measured up to a maximum of 6 g. Notably, the blood pressure measurement in the patient with maximal proteinuria was the highest reading recorded at diagnosis.

Levels of HIF-1 α transcription factor were observed to reflect failed pseudovasculogenesis in mothers with pre-eclampsia. The HIF-1 α levels in prenatal blood samples of the mothers with pre-eclampsia were higher compared to levels in postnatal blood samples, achieving a 100% correlation. The percentage reduction of mean HIF-1 α levels postnatally in mothers with pre-eclampsia was 42.81% (Fig. 2).

The values attained suggest that the levels of HIF-1 α transcription factor in the blood of mothers with pre-eclampsia decreased following delivery of the placenta, supporting the assumption that the placenta could be responsible for this particular disease (1,4). In normal mothers the HIF-1 α levels were comparatively low in pre- as well as postnatal blood samples, demonstrating similar mean values (0.77 and 0.81, respectively).

Discussion

Placental weights of the pre-eclamptic mothers were lower compared to placental weights of normal mothers. This may be attributable to placental ischaemia due to aberrant pseudovasculogenesis. This finding correlated with those of Pandit *et al* (3) in their study on placental weights in 100 cases of pre-eclamptic placentae (3).

The presence of HIF-1 α in ischaemic environments and its increased levels in the blood of mothers with pre-eclampsia

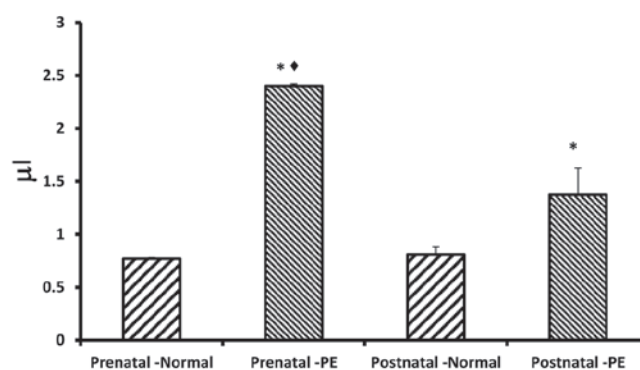


Figure 2. Hypoxia-inducible factor-1 α (HIF-1 α) transcription factor levels in pre- and postnatal blood samples in normal mothers and mothers with pre-eclampsia (PE). * $P < 0.05$, compared to prenatal normal group; ** $P < 0.05$, compared with postnatal PE.

are compelling features to study this transcription factor as well as its role as a predictor of pre-eclampsia.

The presence of HIF-1 α transcription factors, albeit in extremely low quantities, may present a debate regarding the utility of this transcription factor as a predictor for pre-eclampsia if measured in early pregnancy. However, it suggests that should the levels of this transcription factor be measured more frequently, a steady increase of HIF-1 α levels could still be commensurate with a potential development of pre-eclampsia at a later trimester. Further research should be conducted as a population-based study on a larger research cohort.

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