Research Article

Role of nitric oxide in the pathophysiology of pregnancy-induced hypertension

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ABSTRACT

Background: Pregnancy-induced hypertension (PIH) is a major cause of morbidity and mortality during pregnancy. Previous research suggests that endothelial dysfunction is important in the pathogenesis of PIH and may lead to alterations in nitric oxide (NO) synthesis. As endothelial cell damage is considered pivotal in the pathogenesis of pre-eclampsia, this study was initiated to determine whether NO production is decreased in patients with PIH. **Objective:** The objectives of this study were to determine the role of NO levels on the increased vascular resistance in the pathophysiology of PIH. **Materials and methods:** A case–control study was conducted. A total of 60 women in the second trimester of pregnancy with PIH and 60 healthy, normotensive women in second trimester matched with respect to maternal age, gestational age, and body mass index were selected. The resting blood pressure of the subjects was recorded on 2 consecutive days, and the average of the two values was recorded. Fasting blood samples of the subjects was obtained for the estimation of NO levels. **Results:** The mean serum NO levels of both the groups were compared. A decrease was observed in the mean serum NO levels (μM) in subjects with PIH (18.5 ± 5.8) compared with the controls (36.9 ± 3.9). The difference was statistically significant at $P < 0.05$. **Conclusion:** The present study shows a significantly less level of serum NO in women in their second trimester of pregnancy with PIH compared to the controls. This finding may be one of the major clues in unravelling the role of endothelial dysfunction in the pathophysiology of PIH and hence aid in its management.

KEY WORDS: Nitric Oxide; Pregnancy-Induced Hypertension; Primiparous; Endothelial Dysfunction

INTRODUCTION

Pregnancy-induced Hypertension (PIH)

It is defined as the development of new onset of hypertension after 20 weeks of gestation without the onset of proteinuria or other features of pre-eclampsia.[1] A pregnant female is said to have PIH if her blood pressure is higher than 140/90 mm of Hg, measured on two separate visits or more than 6 h apart.[2]

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Pre-eclampsia

It is defined as a combination of PIH plus proteinuria (i.e., >300 mg of protein in a 24-h urinary sample).

Severe Pre-eclampsia

It occurs when blood pressure exceeds 160/110 mmHg, with added abnormal signs and symptoms such as pedal edema.

Eclampsia

It is defined as PIH plus proteinuria plus tonic-clonic seizures appearing in a pregnant female. Pre-eclampsia and eclampsia are at times treated as components of a common syndrome.[3]

In spite of being the important cause of maternal and infant mortality, the factors that are responsible for the development

of PIH are very uncertain. An originating episode in PIH has been proposed to be a decrease in the placental perfusion that primes an extensive vascular endothelial dysfunction by certain unclear mechanisms. Certain studies propose the absence of the normal fall in the blood pressure seen in pregnancy in PIH. Some studies also propose that the increase in blood pressure is mainly due to placental hyperresponsiveness or placental vasoconstriction. Although the causes of PIH have not been fully interpreted, various mechanisms such as the renin-angiotensin-aldosterone system, local mediators, and platelets have all been associated.[4]

Nitric oxide (NO) which is a powerful mediator released by vascular endothelial cells impedes adhesion and aggregation of platelets. It also produces vasodilation of the placental bed. The primary objective of the present study was to find whether lower levels of NO in circulation could be associated with the increased placental vascular resistance and hence the high blood pressures observed in PIH.

MATERIALS AND METHODS

The present study was conducted at the at Government Kilpauk Medical College Hospital, Chennai. After obtaining the permission from the Institutional Ethics Committee, 60 primiparous women in the second trimester of pregnancy with PIH and 60 healthy, normotensive primiparous women in second trimester matched with respect to maternal age, gestational age, and body mass index were selected. The scope of the study was explained to all the subjects, and an informed written consent was obtained. The women with PIH had persistently (measured on two separate occasions, more than 6 h apart) elevated blood pressure readings of ≥140 mmHg systolic and 90 mmHg diastolic. Subjects with proteinuria of ≥300 mg in 24 h were excluded from the study. Women with multiple pregnancies, other pregnancy-related complications such as gestational diabetes mellitus, and other pre-existing diseases were excluded from the study.

Study Design

This was cross-sectional case - control study

Collection of Data

The resting blood pressure of the subjects was recorded on 2 consecutive days, and the average of the two values was recorded. Fasting blood samples of the subjects were obtained for the estimation of serum NO levels. The serum levels of NO was measured using enzyme-linked immunosorbent assay kits, namely serum NO determination, using kit supplied by Intron Bio. The NO estimation kit is on the basis of diazotization (Griess method) technique and is capable of measuring *in vitro* concentration of NO. This estimation kit facilitates to overcome technical hitches in detecting NO attributable to the brief half-life of almost 5 s. NO concentration is indirectly measured by means of accurately quantifying the levels of nitrite (NO_2^-), the derivative of NO in live tissues. The chemical basis of the test is a color change that takes place when the compound naphthyl ethylenediamine is added to the offshoot of the reaction amid sulfanilamide and nitrite.

RESULTS

The mean serum NO levels of both the groups were compared. A decrease was observed in the mean serum NO levels (μM) in subjects with PIH (18.5 ± 5.8) compared with the controls (36.9 ± 3.9). Student's *t*-test was used for the comparison of parameters. The difference was statistically significant at $P < 0.05$ [Figure 1].

DISCUSSION

The present study shows a significantly less level of serum NO in women in their second trimester of pregnancy with PIH compared to the controls.

Our study is supported by a study finding that inhibiting the synthesis of NO during the gestational period in rats resulted in high blood pressure and pre-eclampsia like features.[4,5] Furthermore, in a similar study, it was proven that, in pregnant rats, the blockage in the production of NO synthase enzyme leads to a condition that is similar to PIH and the features were reverted by infusion of L-arginine.[6] This finding also supports the results of our study. A research study where small-sized blood vessels were isolated from pregnant women with pre-eclampsia and established an impaired endothelial-mediated vasodilatation[7] is also in concurrence with our results. However, the results of our study and studies of serum levels of metabolites of NO and the levels of cGMP through which NO exerts its action have been inconsistent,[8] wherein an increase in NO metabolites were reported. Our study is also supported by another article which reports previous

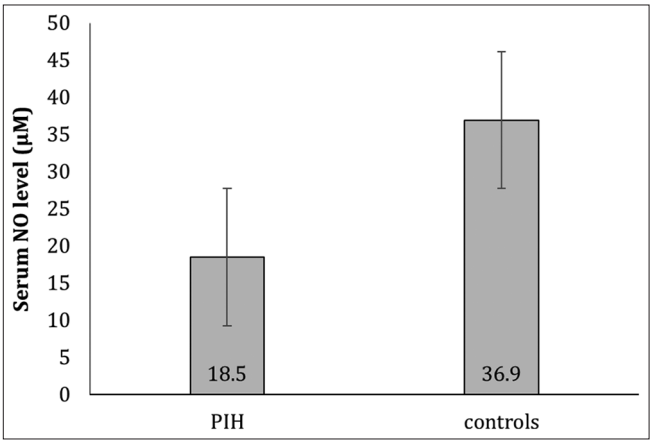

Figure 1: Serum nitric oxide levels (μM) in subjects with pregnancy-induced hypertension compared with the controls

study which found that lower levels of blood pressure were associated with higher levels of serum NO in elderly subjects.[9] Other similar studies also implicate the deficiency of or impaired responsiveness to NO in the genesis of pre-eclampsia[10,11] which lend support to our findings. A recent finding suggests that NO synthase in the placenta has been found to be reduced in pre-eclampsia as well as the release of vasodilators (endotheliumderived relaxing factor) from umbilical vessels[12,13] which strengthens our hypothesis.

The sample size of the study is less, and the findings may not represent the findings in the general population. Furthermore, prospective studies on interventions for improving NO levels during pregnancy, such as physical activity, diet, and mild aerobic training, could enhance the value of this study.

To conclude, PIH is a major cause of morbidity and mortality during pregnancy, affecting both the mother and the fetus. It is of great public health importance, and an exact pathophysiology has to be identified for its prevention, early diagnosis, and management.

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