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Differential levels of long chain polyunsaturated fatty acids in women with preeclampsia delivering male and female babies

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ABSTRACT

Maternal long chain polyunsaturated fatty acids (LCPUFA) play a key role in fetal growth and development. This study for the first time examines the maternal and cord LCPUFA levels in preeclamptic mothers delivering male and female infants. In this study 122 normotensive control pregnant women (gestation ≥ 37 weeks) and 90 women with preeclampsia were recruited. Results indicate lower maternal plasma docosahexaenoic acid (DHA) levels ($p < 0.05$) in women with pre-eclampsia delivering male babies as compared to normotensive control women delivering male babies. Similarly, cord nervonic acid levels were lower ($p < 0.01$) in women with preeclampsia delivering male babies as compared to normotensive control group. However, cord nervonic acid levels were comparable in women with preeclampsia and normotensive control women delivering female babies. This data suggests that male babies born to mothers with preeclampsia may be at an increased risk of developing neurodevelopmental disorders as compared to female babies. Future studies need to follow up both male and female children born to mothers with preeclampsia since altered levels of LCPUFA at birth may have differential implications for the growth and development.

1. Introduction

Preeclampsia a leading cause of maternal and fetal mortality and morbidity worldwide is widely believed to be due to improper placentation [1]. Our earlier cross sectional studies have demonstrated the association of altered maternal micronutrition especially long chain polyunsaturated fatty acids (LCPUFA) status in women with preeclampsia [2,3]. The two types of LCPUFA i.e. omega-3 and omega-6 fatty acids which are components of cell membranes and are important for fetal growth and development [4,5]. Linoleic acid (LA) an omega-6 fatty acids and alpha-linolenic acid (ALA), an omega-3 fatty acid are converted to arachidonic acid (AA) and docosahexaenoic acid (DHA) by the series of elongation and desaturation using elongases and desaturases enzymes [6,7].

In humans AA and DHA play a vital role in brain development [8,9]. In childhood, omega-3 fatty acids especially DHA is reported to influence cognitive development [10,11]. Nervonic acid an omega-9 fatty acid is a component of membrane sphingolipids and phosphatidylethanolamines [12] and recent studies suggest its involvement in learning and memory [13]. These fatty acids are of significance since children born to mothers with preeclampsia are reported to be at an increased risk of developing neurodevelopmental disorders in later life [14–16]. Reports indicate that many early onset neurodevelopmental disorders are male-biased, that is they occur significantly more often in males than females [17].

Recent studies indicate that the gender distribution needs to be taken into account while assessing data on fatty acid composition [18]. Females are reported to have a higher DHA status than males [19]. Studies also suggest that sex hormones may influence the enzymatic synthesis of LCPUFA, which may lead to sex-specific differences in LCPUFA status [20]. Reports indicate that there is an association between plasma and tissue fatty acid composition and circulating sex hormone concentrations, estrogen stimulates, whereas testosterone inhibits, the conversion of essential fatty acids into their longer-chain metabolites [21].

Preeclampsia originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction [22]. It has been suggested that hypoxia, placental oxidative stress, excessive or atypical maternal immune response to trophoblasts, exaggerated inflammation may play a role

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in poor placentation in preeclampsia [23]. Sex specific alterations in placental genes involved with growth and inflammation are reported in cases of maternal hypoxia suggesting that aberrations in placental functions can occur in a sex specific manner [24]. Further, recent reports also indicate that there exists a sex specific difference in feto-placental perfusion indices [25].

However it is unclear whether the sex of the fetus is associated with maternal and cord levels of LCPUFA levels in preeclampsia and normotensive control. The present study was carried out to test the hypothesis that "LCPUFA levels in mothers with pre-eclampsia delivering male and female babies and their cord samples may be different".

2. Materials and methods

2.1. Study subjects

This study was conducted at the Dept of Obstetrics and Gynecology, Bharati Hospital, Pune during the year 2011–2013. The research protocol was approved by the Institutional Ethical Committee. A written consent was taken from women participating in the study. Healthy pregnant women with no medical or obstetrical complications and delivered at term (total gestation $\geq$ 37 weeks) were recruited for the normotensive control (normotensive control, $n=122$) group study. Women with pre-eclampsia (preeclampsia; $n=90$) were also recruited. Further, these groups were classified as women delivering male (normotensive control = 69, preeclampsia = 54) and female (normotensive control = 53, preeclampsia = 36) babies.

Preeclampsia was defined by systolic and diastolic blood pressures (BP) greater than 140/90 mmHg respectively, with the presence of proteinuria (> 1+ or 300 mg) on a dipstick test and recorded at two time points > 6 h apart. This diagnosis of pre-eclampsia and the inclusion exclusion criteria have been reported by us earlier [2,3,26,27]. Birth outcome parameters like baby weight, length, head and chest circumference were recorded within 1 h after birth.

The statistical power was calculated based on our earlier study in preeclampsia [28] where we have reported significant group differences in homocysteine levels from 49 preeclamptic and 57 normotensive women ($p < 0.01$).

2.2. Sample collection and processing

10 ml of maternal venous blood was collected into the ethylenediamine tetra-acetic acid (EDTA) vials just before delivery. All blood samples were immediately layered on histopaque (a density gradient obtained from Sigma-Aldrich) and centrifuged at 2000 rpm for 30 min to separate the plasma and erythrocytes. The erythrocytes aliquots were stored at −80 °C until further analysis.

2.3. Plasma fatty acid estimation

The procedure for fatty acid analysis used in this study has been reported by us earlier in separate studies [3,26,28,29]. Briefly, transesterification of plasma and erythrocyte fraction was carried out using hydrochloric acid-methanol.

These were separated using a Perkin-Elmer gas chromatograph (SP 2330, 30 m capillary Supelco column). Helium was used as the carrier gas at a flow rate of 1 ml/min. Oven temperature was held at 150 °C for 10 min, programmed to rise from 150 °C to 220 °C at 10 °C/min and held at 220 °C for 10 min. The detector temperature was 275 °C and the injector temperature was 240 °C. Retention times and peak areas were automatically computed. Peaks were identified by comparison with standard fatty acid methyl esters (Sigma). Fatty acids were expressed as g/100 g fatty acid i.e. percentage of total fatty acids.

Omega-3 fatty acids included ALA, eicosapentaenoic acid (EPA) and DHA while the omega-6 fatty acids included LA, γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA), AA and docosapentaenoic acid (DPA). Saturated fatty acids (SFA) included myristic acid, palmitic acid and stearic acid while the monounsaturated fatty acids (MUFA) included myristoleic acid, palmitoleic acid, oleic acid and nervonic acid.

2.4. Statistical analysis

Values are expressed as mean ± SD. The data were analyzed using SPSS/PC+ statistical package (Version 20, Chicago IL). Data was checked for normal distribution by testing for skewness and kurtosis. Skewed variables were transformed to normality using the following transformations: log to the base10 (DHA, AA, nervonic acid, ALA, LA). Mean values of the estimates of various parameters for preeclampsia were compared with those of normotensive control group at conventional levels of significance ($p < 0.05$, $p < 0.01$) using one way ANOVA method. The interaction between the variables (DHA, AA, nervonic acid, ALA, LA, omega-3 and omega-6) with gender in each group was analyzed by two way ANOVA method.

3. Results

3.1. Maternal and neonatal characteristics

The systolic and diastolic blood pressures were higher in women with preeclampsia as compared to the normotensive control women ($p < 0.01$). Baby weight, length, chest circumference and head circumference were lower ($p < 0.01$) in the pre-eclampsia group as compared to normotensive control group (Table 1).

3.2. Maternal plasma fatty acid levels in different groups

Maternal plasma MUFA levels were higher in women with preeclampsia ($p < 0.01$) as compared with women in normotensive control group. However, no change was seen in case of SFA in the preeclampsia group. Further, ALA ($p < 0.05$), DHA ($p < 0.01$) and total omega-3 fatty acids ($p < 0.01$) was lower in the pre-eclampsia group as compared with normotensive control women. There was no difference in case of maternal plasma nervonic acid (Table 2).

3.3. Maternal plasma fatty acids in women delivering male and female babies

MUFA levels were higher ($p < 0.01$) in women with preeclampsia delivering male babies as compared with the women delivering male babies in normotensive control group. There was no change in case of SFA levels in any of these groups. DHA levels were lower only in women with preeclampsia delivering male babies as compared to those from normotensive control group ($p < 0.05$) while omega-3 fatty acid levels were lower in women with preeclampsia delivering male ($p < 0.05$) as compared to normotensive control women delivering male babies. Omega-3 fatty acid levels were also lower in female babies ($p < 0.05$) when compared to respective women from normotensive control group. There was no change in case of omega-6 fatty acids and nervonic acid levels (Table 3).