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Preeclampsia alters milk neurotrophins and long chain polyunsaturated fatty acids

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ABSTRACT

Objective: To examine the levels of breast milk neurotrophins 1.5, 3.5, and 6 months of lactation and long chain polyunsaturated fatty acids (LCPUFA) at day 3, 1.5, 2.5, 3.5 and 6 months of lactation in mothers with preeclampsia and compare them with normotensive women. Their associations with growth parameters in children are also examined.
Methods: Women with preeclampsia ($n = 101$) and normotensive women ($n = 144$) with singleton pregnancies were recruited for this study. Milk samples were collected and anthropometry was recorded at the first 6 months. The LCPUFA composition of milk samples was analyzed by using gas chromatography at all time points and neurotrophins were analyzed at 1.5, 3.5 and 6 months by Emax Immuno Assay System using Promega kits.
Results: Milk DHA levels were higher at day 3 (9.5%), and 1.5 (23%) and 3.5 (40%) months in mothers with preeclampsia as compared to controls. Milk nerve growth factor (NGF) levels were lower in preeclampsia group as compared to control group at 1.5 (20%) and 3.5 months (27.7%). Milk brain derived neurotrophic factor (BDNF) levels were lower at 1.5 months (10.5%) in the preeclampsia group as compared to control group.
Conclusion: The present study suggests that there is a differential regulation of DHA and neurotrophins in breast milk in preeclampsia and are associated with growth parameters of children. Future studies should explore the associations between milk LCPUFA, neurotrophins with neurodevelopment in children.

1. Introduction

Human milk has been reported to contain wide range of nutrients and several components like hormones (Kulski and Hartmann, 1981), growth factors (Donovan and Odle, 1994), cytokines (Srivastava et al., 1996), immunological components (Jackson and Nazar, 2006), immunomodulatory factors (Bertino et al., 2012) and fatty acids (Agostoni et al., 2005) which play a vital role in the growth and development of the infant (Serpero et al., 2012). Pregnancy complications such as pregnancy induced hypertension (PIH) (Cunningham et al., 1993); preeclampsia (Erbağci et al., 2005) and gestational diabetes (Butte et al., 1987) are known to affect lactogenesis (Kaushik et al., 2002). Babies born to mothers with preeclampsia are at high risk for metabolic and cognitive disorders (Many et al., 2003) due to neurodevelopmental impairment in later life (Streimish et al., 2012).

Evidence suggests that long-term breastfeeding is associated with lower hyperactivity symptoms (Julvez et al., 2007); improved neuropsychological and socio-behavioral outcomes and cognition in children (Keim et al., 2012; Hadders-Algra, 2011; Jensen and Lapillonne, 2009; Daniels and Adair, 2005; Clark et al., 2006; Hüppi, 2008). A review has suggested that milk long chain polyunsaturated fatty acids (LCPUFA), specifically docosahexaenoic acid (DHA) and arachidonic acid (AA), many growth factors and hormones influence infant's growth, development and cognitive performance (Yum, 2007). Human milk polyunsaturated fatty acids (PUFA) are either derived from the diet or are synthesized from endogenous precursor fatty acids (Sauerwald et al., 2001) and are required in adequate quantities for optimal growth and development of infants (Xiang et al., 2005). However, reports on milk LCPUFA influence on infant growth are controversial (Tinoco et al., 2009; Scholtens et al., 2009).

Reports also indicate that LCPUFA especially DHA regulates the levels of neurotrophins (Rao et al., 2007; Wu et al., 2004). Milk

Abbreviations: AA, arachidonic acid; BDNF, brain derived neurotrophic factor; DHA, docosahexaenoic acid; LCPUFA, long chain polyunsaturated fatty acids; NGF, nerve growth factor.

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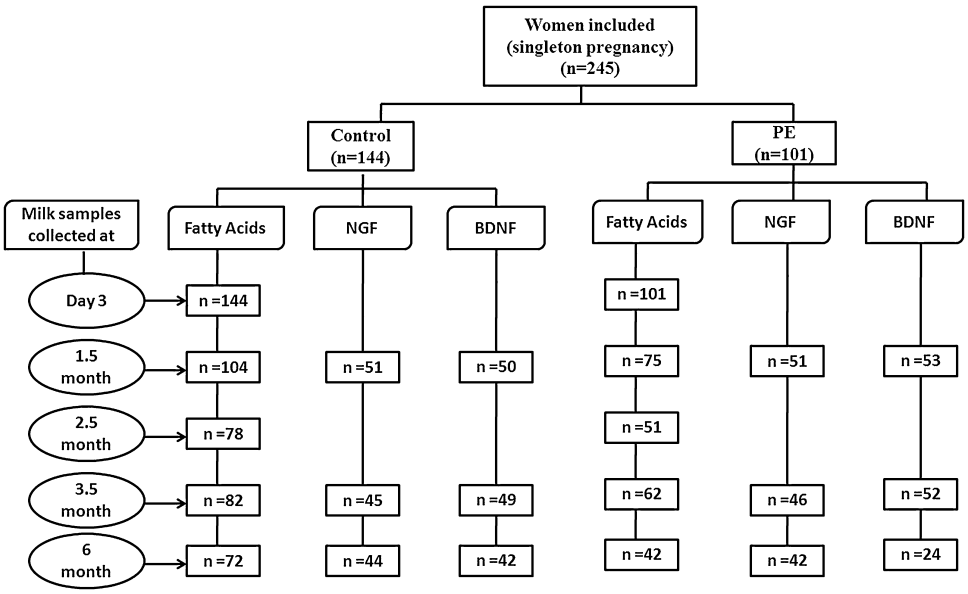

Fig. 1. Flow chart for number of samples analyzed at various time points. PE: preeclampsia; BDNF: brain derived neurotrophic factor; NGF: nerve growth factor.

growth factors such as brain derived neurotrophic factor (BDNF) (Li et al., 2011) and nerve growth factor (NGF) (Banapurmath et al., 1996) are known to play a critical role in the development and maintenance of the nervous system.

Recent reports also indicate that the milk components change over the course of lactation due to time dependent programmed requirement for the child development (Ballard and Morrow, 2013; Erbağci et al., 2005; Li et al., 2011). Milk fatty acid profile found to be affected by maternal dietary and life style factors of mother (Antonakou et al., 2012). We have earlier reported that milk fatty acids and neurotrophins levels are altered at d3 of lactation in preeclampsia (Dangat et al., 2010, 2013) which may affect the milk quality and postnatal programming of child. However, it is unclear whether these vital constituents remain altered during the complete duration of lactation. Thus, the present study for the first time examines simultaneously the levels of human milk fatty acids and neurotrophins in mothers with preeclampsia and compares them with controls at various time points during lactation and also examines their association with growth of the infant.

2. Materials and methods

This study was conducted at the Departments of Pediatrics and Obstetrics & Gynecology, Bharati Hospital, Pune during the year 2011–2012. Singleton pregnant women with preeclampsia ($n = 101$) and without preeclampsia (controls) ($n = 144$) were recruited at the time of delivery for this prospective study. Mothers and their babies were followed-up at day 3, and 1.5, 2.5, 3.5 and 6 months post delivery. The anthropometry (weight and length, head and chest circumference) of the infant was recorded at all time points during lactation. Fig. 1 shows the number of milk samples analyzed for fatty acids and neurotrophins at various time points during lactation.

This study was approved by Institutional Ethical Committee and a written informed consent was taken from each subject. Subjects were excluded from the study if there was evidence of other pregnancy complications like multiple gestation, chronic hypertension, type I or type II diabetes mellitus, seizure disorder, renal or liver disease. Pregnant women with alcohol or drug abuse were also excluded from the study. The control group consisted of pregnant women with no medical or obstetrical complications. Preeclampsia was diagnosed by the criteria discussed by us in a number of our studies reported earlier (Kilari et al., 2011; Kulkarni et al., 2010). Briefly, preeclampsia was defined by systolic and diastolic blood pressures greater than 140 and 90 mmHg respectively with proteinuria in a dipstick test. The oil consumption per month has been recorded at the time of recruitment. Treatment of preeclamptic women included antihypertensive drugs and arginine supplementation. In severe preeclamptic cases, $MgSO_4$ was given intravenously. It is unlikely that these would affect BDNF status.

2.1. Collection of milk samples

Human milk sampling was done at all time points during lactation. The samples were collected when the babies come for vaccination at 1.5, 2.5 and 3.5 months of age. Samples of breast milk (2 ml) were taken at the end of the baby's being breast-fed and collected into cryo vials and were stored at −80 °C.

2.2. Fatty acid analysis

Milk samples were analyzed at all time points by the gas chromatography and have been described by us earlier (Dangat et al., 2010). Fatty acids were expressed as g/100 g fatty acid. A total of 15 fatty acids were estimated. Saturated fatty acids include myristic acid, palmitic acid and stearic acid while monounsaturated fatty acids include myristoleic, palmitoleic, oleic and nervonic acids. The omega 3 fatty acids included alpha linolenic acid (ALA), eicosapentaenoic acid (EPA) and DHA while omega 6 fatty acids included linoleic acid (LA), gamma linolenic acid (GLA), di-homo-gammalinolenic acid (DGLA), docosapentaenoic acid (DPA) and AA.

2.3. Neurotrophins analysis

Milk neurotrophins at day 3 has been published recently (Dangat et al., 2013). Milk neurotrophins at 1.5, 3.5 and 6 months of lactation were analyzed by Emax Immuno Assay System using the Promega kits for BDNF (Hornbeck et al., 1994) and NGF (Zettler et al., 1996) which has been described by us earlier (Dangat et al., 2013). The amount of BDNF and NGF was expressed as pg/ml.