Original Article

Maternal total homocysteine concentration and neonatal size in India

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The smallness of Indian babies is ascribed to small maternal size and their chronic under nutrition. Micronutrient nutrition of the mother may be particularly important. We investigated the relationship between maternal circulating concentrations of total homocysteine (tHcy), vitamin B12 and folate and offspring size at birth. Mothers of full term small for gestation age babies (SGA, gestation and sex specific birth weight <10th centile, *N* = 30) and mothers of appropriate for gestational age babies (AGA, >10th centile, *N* = 50) were compared for their body size, plasma tHcy, vitamin B12 and red cell folate concentration at 28week gestation. Mothers of SGA babies were lighter and shorter than those of AGA babies (*P* <0.05, both) and had higher plasma tHcy concentration (*P*<0.01). Total homocysteine concentrations were inversely related to plasma vitamin B12 and red cell folate concentrations (r = ~ -0.5, *P* <0.01, both). Seventy percent of the women had a low vitamin B12 status (plasma vitamin B12 <150 pmol/L) but none were folate deficient (red cell folate <283 nmol/L). Higher maternal plasma tHcy concentration was significantly associated with lower offspring birth weight (r=-0.28, *P*<0.05 adjusting for maternal height, weight, gestation at delivery and the baby's gender), this effect was reduced by adjustment for red cell folate concentration. We conclude that maternal vitamin B12 deficiency reflected in plasma tHcy concentration contributes to small size of Indian babies.

Key Words: total-Homocysteine, vitamin B12, folate, neonatal size, India

Introduction

The small size of Indian babies is usually ascribed to the small size and 'chronic undernutrition' of Indian mothers[1] though there is no information on specific nutrients that may be responsible. Indians have high plasma total homocysteine (tHcy) concentrations due to low vitamin B12 status,[2] folate deficiency was relatively rare in this study. Vitamin B12 and folate play an important role in nucleic acid metabolism, cell growth and proliferation and are important determinants of fetal growth.[3] We investigated the association between maternal plasma tHcy concentration and offspring size at birth in the Pune Maternal Nutrition Study (PMNS). This is a prospective population-based study conducted in 6 villages near Pune, which included careful measurements of maternal size and nutrition, and newborn size. Seven hundred and seventy live, singleton, normal babies were delivered (633 full term). Maternal blood samples were stored at -80^{0}C between 1993-96. Red cell folate concentrations were measured in the original study.[4] In 2001 we used stored samples to measure plasma tHcy (IMx, Abbott Laboratories, IL, USA) and vitamin B12 (Radioimmunoassay, Becton Dickinson, UK) in a subset of women: this included mothers of full term small for gestational age babies (SGA, gestation and sex specific birth weight <10th centile, *N*=30) and mothers of appropriate for gestational age babies (AGA, >10th centile, *N*=50). This relatively small number was dictated by the cost of the assays. We appreciate the limited power of this study due to small number of subjects, but feel that the results are significant enough to be reported pending a larger study. The study was approved by the Ethical Committee of the King Edward Memorial Hospital Research Centre, each subject signed an informed consent.

Mothers of SGA babies were lighter and shorter than those of AGA babies (*P*<0.05, both) and had higher plasma tHcy concentration at 28wks gestation (*P*<0.01) (Table 1). There was no significant difference in the socio-economic score of these mothers. Total homocysteine concentrations were inversely related to plasma vitamin B12 and red cell folate concentrations (r = ~ -0.5, *P*<0.01, both) but not to maternal size. Seventy percent of the women had a low vitamin B12 status (plasma vitamin B12 <150 pmol/L) but none were folate deficient (red cell folate <283 nmol/L). Nearly half of the mothers never ate meat, fish or eggs and a third never drank milk.

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Table1. Maternal and neonatal characteristics

Variable	*SGA* *N* = 30	AGA *N* = 50	*P* value
Maternal characteristics			
Before pregnancy			
Age (years)	22 (5)	22 (4)	0.52
Weight (kg)	39.0 (5)	42.0 (6)	<0.05
Height (cm)	150 (5)	152 (5)	<0.05
18 weeks gestation			
Red cell folate (nmol/L)	840 (744, 965)	951 (693, 1359)	0.18
28 weeks gestation			
Weight gain (kg)	4.7 (2.2)	5.2 (3.0)	0.33
† Red cell folate (nmol/L)	912 (744, 1194)	1053 (784, 1625)	0.14
† Plasma vitamin B12 (pmol/L)	106 (87, 128)	124 (100,150)	0.28
‡ Plasma vitamin B12 < 150 pmol/L	23 (77)	33 (66)	0.94
† Plasma tHcy (μmol/L)	7.2 (5.4, 9.8)	5.5 (4.4, 6.7)	<0.01
Neonatal characteristics			
‡ Boys	15 (50)	25 (50)	
Weight (kg)	2.0 (0.2)	2.8 (0.3)	<0.001
Placental weight (g)	278 (65)	392 (85)	<0.001

Values are mean (SD). ‡ *N* (%). † geometric mean (IQR).
P value tested using student t test or chi-square test.

Table 2. Multiple linear regression models to predict off-spring birth weight

Models	Variables in the model	β	*P* value
1	Maternal tHcy (μmol/L)	-431.7	0.001
2	Maternal tHcy (μmol/L)	-398.3	0.002
	Maternal height (cm)	31.8	0.001
3	Maternal tHcy (μmol/L)	-357.3	0.005
	Maternal height (cm)	24.8	0.019
	Maternal weight (kg)	13.7	0.15
4	Maternal tHcy (μmol/L)	-298.6	0.015
	Maternal height (cm)	28.5	0.006
	Maternal weight (kg)	9.7	0.29
	Gestational length (week)	116.7	0.007
5	Maternal tHcy (μmol/L)	-280.3	0.027
	Maternal height (cm)	27.9	0.006
	Maternal weight (kg)	10.5	0.29
	Gestational length (week)	116.9	0.007
	Baby's gender	0.1	0.99
6	Maternal tHcy (μmol/L)	-239.6	0.10
	Maternal height (cm)	26.3	0.02
	Maternal weight (kg)	9.5	0.32
	Gestational length (week)	122.6	0.008
	Baby's gender	15.9	0.88
	Red cell folate (nmol/L)	171.0	0.23

Plasma tHcy concentration and other predictors of offspring birth weight were serially included in the models.

Maternal plasma vitamin B12 concentration was not related to offspring size but red cell folate concentration was directly related (r=0.3, *P*<0.01). Plasma vitamin B12 concentration in our study women was very low and therefore it was difficult to show any relationship with off-spring weight. We performed a multivariate analysis to predict birth weight. Variables which were significantly different in the mothers of AGA and SGA babies were included as predictors in the multiple regression analysis. Table 2 shows effect of maternal plasma tHcy concentration on birth weight with and without adjustment for confounders. Higher plasma tHcy concentrations were significantly associated with lower birth weight (r=-0.28, *P*<0.05 adjusting for maternal height, weight, gestation at delivery and the baby's gender). Further adjustment for red cell folate concentration reduced this significance, indicating importance of maternal vitamin nutrition in this relationship. Our data confirm reports showing an inverse association between maternal tHcy concentration and the size of the offspring at birth.[5] Elevated tHcy may impair fetal growth by affecting maternal cardiovascular adjustments in pregnancy as well as the placental and fetal circulations.[6] In the West, high tHcy concentrations are usually due to folate deficiency but few of our mothers were folate deficient as measured by erythrocyte red cell folate. On the other hand the majority had poor vitamin B12 status. This traps folate as tetrahydrofolate (THF) and makes it unavailable for metabolic use. This could create a functional folate deficiency despite normal circulating levels which may have a direct effect on fetal growth.[7]

Low vitamin B12 status has been demonstrated in Indians living in India as well as those living abroad.[8,9] Indians may be born with low vitamin B12 status due to low maternal levels and then continue to have low status due to vegetarian diet and malabsorption due to 'tropical sprue'.[10,11] Vitamin B12 deficiency in Indian mothers and associated functional folate deficiency could be the first example of a nutrient deficiency which links poor fetal growth with increased risk of cardiovascular disease in later life because hyperhomocysteinemia is a recognized cardiovascular risk factor. Vitamin B12 deficiency is poorly appreciated by the medical profession in India and the National Nutritional Anemia Prophylaxis Program advocates only iron and folate treatment for pregnant women.[12] We expect our results to stimulate more studies of vitamin B12 and folate status in Indian women in relation to fetal growth and future cardiovascular risk.

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