Original Article

Breast Feeding and Insulin Levels in Low Birth Weight Neonates: A Randomized Study

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ABSTRACT

Objective. To evaluate the influence of early infancy feeding practices on fasting insulin levels, as marker of insulin resistance, in low birthweight neonates.

Methods. Eighty successive low birth weight (<2.5 kg) neonates <10 days of age born at >38 wk of gestation at this tertiary care centre, were successively invited for participation in the study; parents of 52 (65%) consented to participate. Group 1 children (n=26) were randomized to receive only breast feeding and Group 2 (n=26) received fortified breast feeding with a commercially available human milk fortifier. Routine anthropometry and evaluation of health status was performed. The babies were followed-up every 15 day up to three months. 4-hour fasting glucose and insulin levels were measured at baseline and at 3 month. Statistical analyses were performed using t-test and Mann-Whitney test.

Results. In excusively breast-fed Group 1 neonates *vs* Group 2 the mean birthweight was similar (1.99±0.23 *vs* 1.87±0.30 kg). There was no difference in body length, head circumference and chest circumference. Mean hemoglobin levels, fasting glucose (63.9±9.8 *vs* 64.3±8.0 mg/dl) and fasting insulin levels (1.44±1.19 *vs* 1.73±1.38 µU/ml), were also similar. At three month follow-up in Group 1 children receiving exclusive breast feeding, there was significantly lower weight as compared to Group 2 (3.40±0.3 *vs* 4.75±0.5 kg, p<0.01). This was associated with significantly lower fasting glucose (79.0±9.4 *vs* 85.6±8.4 mg/dl) and fasting insulin levels (6.95±4.27 *vs* 15.73±3.29 µU/ml) (p<0.001).The difference persisted even after adjustment for weight gain in Group 2 (weight adjusted insulin 11.26±3.3 µU/ml; p<0.001).

Conclusions. Low birthweight neonates fed fortified breast milk had greater fasting insulin levels compared to those with exclusive breast feeding, at three month of age. The difference persisted after adjustment for excessive gain in fortified milk fed neonates and, suggests adverse glucometabolic programming. **[Indian J Pediatr 2010; 77 (5) : 509-513]** *E-mail: mukeshg4@gmail.com*

Key words: *Insulin-levels; Low birth weight; Fortified breast milk*

Low birthweight predisposes to adult diabetes and cardiovascular diseases.[1,2,3,4] Initial studies from England and Western Europe have shown that adult cardiovascular mortality was significantly greater in those with low birthweight.[1] In these individuals, there is also evidence of peripheral insulin resistance, lower beta cell pancreatic function, central obesity, hypertension, multiple lipid abnormalities and diabetes.[2] Studies have reported that insulin resistance starts in early infancy, tracks through the childhood and manifest as type 2 diabetes in early and mid adulthood.[4] Similar results have been reported from India.[5,6,7,8] Slow and steady weight gain in childhood is associated with lower incidence of impaired glucose tolerance while a rapid weight gain especially in the first two years of life is associated with significantly greater glucose intolerance.[1,3,4,9,10] Recent data on influence of nutrient excess in early infancy are conflicting. For instance, faster growth in premature children was not associated with mortality from cardiovascular disease in a Finnish cohort but was associated with later cardiovascular risk factors such as endothelial dysfunction, insulin resistance, and dyslipidemia in preterm infants.[11] Similarly, in infants born at term, upward percentile crossing for weight was associated with higher later blood pressure, insulin resistance, and, in two systematic reviews, an increased risk of later obesity.[3,4] Promotion of growth in infancy using nutritional supplements may also be detrimental for later cardiovascular risk. For instance, nutritional supplementation with dried milk powder in infancy has

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been shown to have an adverse long-term effect on or program glucose intolerance, diabetes and higher blood pressure in adulthood.[12-14]

However, most previous studies in humans are observational, and there are a few randomized studies with long-term prospective follow-up that can provide the optimal information about management of infants born small. Influence of early infancy feeding practices, on the development of hyperinsulinemia and insulin resistance, has especially, not been well studied.[1,4] We compared breast feeding with or without supplemental feeding on short term growth parameters and fasting insulin levels as a measure of insulin resistance in low birthweight (small for gestational age) neonates.

MATERIAL AND METHODS

The study was approved by the medical college institutional research review board. Eighty successive low birth weight neonates (<2.5 kg), born at >38 weeks of gestation, less than 10 days of age, and born at this tertiary care centre were enrolled in the study. Parents of 52 children (65%) provided informed consent and assured follow-up and, were included in the study. The inclusion criteria, were children born after 38 wk of gestation; low birth weight, as defined above, and having no inter-current illnesses such as acute of infections or congenital malformations. These children were randomly divided into two groups using simple randomisation protocol (Fig. 1). Group 1 children (n=26), were randomized to recieve exclusive breast feeding and Group 2 children (n=26), received fortified meal in addition, to usual breast feeding. Routine anthropometry, that included measurements of weight, length, head, chest and abdomen circumference was performed by a trained neonatologist, as reported earlier.[15] General evaluation of health status was also performed to exclude any acute illness or congenital abnormality. A 4-hour fasting blood sample was obtained for the estimation of glucose and insulin levels. Glucose was estimated by glucose oxidase peroxidase aminophenazole phenol (GOD-PAP) method, using a commercially available kit (Human mBH, Weisbaden, Germany). Serum insulin was estimated by immunoradiometric assay, using commercial kits. The intra-and inter-assay coefficients of variation for the insulin were 5.2% and 7.3%, respectively; sensitivity was

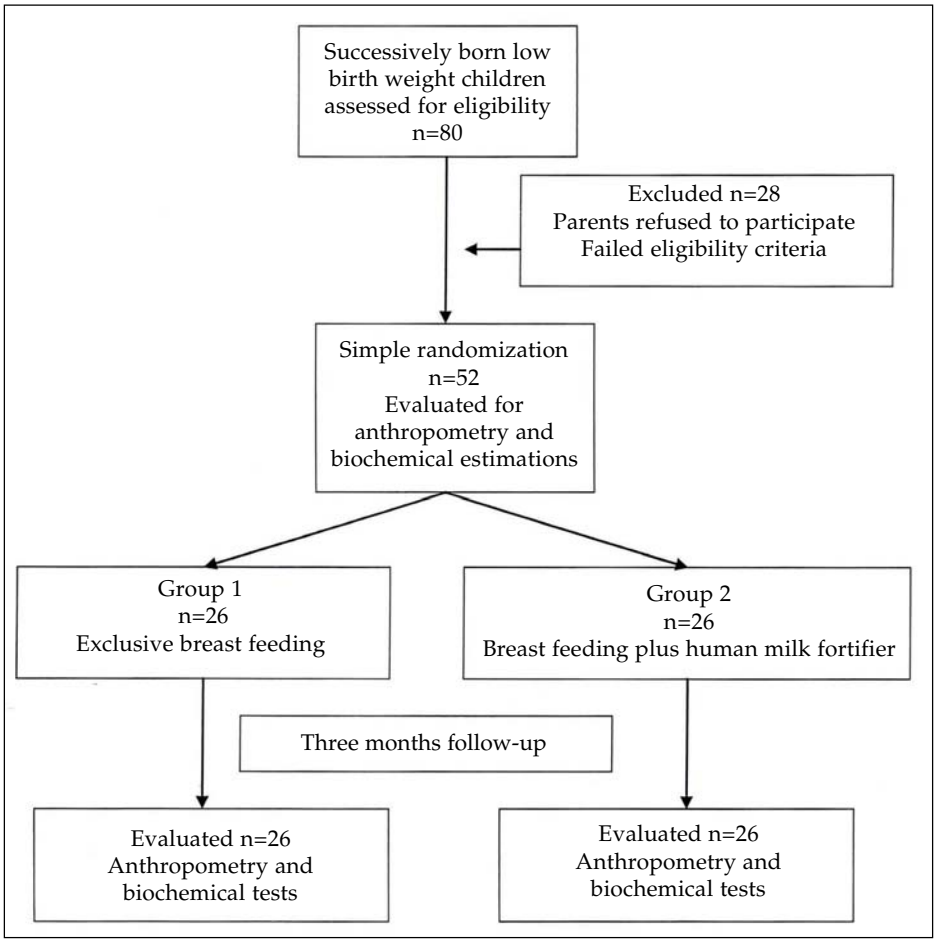

Fig. 1. Study flow chart.

0.8 to 1.2 µU/ml and specificity was 80%. Insulin resistance was not determined, as fasting insulin levels provide similar information.[1]

The mothers of Group 1 children were advised to breast feed the children and to continue it for the study duration. The mothers of Group 2 children were also advised breast feeding but in addition, a fortified meal was advised. A commercially available human milk fortifier was used, which is available as 2 g powder in sachets, containing 0.2 g protein, 0.1 g fat (saturated) and 1.46 g carbohydrates with additional vitamins and minerals. The babies were followed-up every 15 days up to three months and health status was evaluated. Any episodes of inter-current illnesses and other health matters, were inquired. At the end of three months follow up, a detailed history, anthropometry and biochemical estimations for fasting glucose and insulin were performed.

Statistical analyses: Sample size calculation was performed using a commercially available statistical package- Simple Interactive Statistical Analysis *(http://home.clara.net/sisa/)*. For an estimated 100% difference in post-intervention insulin levels in the two groups, two-sided alpha of <0.01 and study power of 90% with a sample size of 15 in each group, was determined. Twenty five subjects in each arm were enlisted to further increase the power of the study and also to counter the effect of lower difference in insulin levels. The data were computed and all analyses performed using SPSS software. Values are reported as mean ± 1 SD. For inter-group comparisons, an unpaired t-test was performed. Insulin levels followed a skewed distribution and pre- and post-intervention values have been compared using a non-parametric Mann-Whitney test. P values less than 0.05 were considered significant.

RESULTS

Various clinical and biochemical indices in the two groups at baseline are shown in table 1. There was no significant difference in weight, length and chest and head circumference. The fasting glucose levels in Group 1 and Group 2 were 63.9±9.8 and 64.3±8.0 mg/dl, respectively (p=n.s.). Mean fasting insulin levels were not significantly different in the two groups and were 1.44±1.19 in Group 1 and 1.73±1.38 µU/ml in Group 2, respectively (p= 0.438). Median insulin and interquartile range (IQR) insulin levels were also not significantly different (Group 1: 1.10, IQR 0.48-2.20; Group 2: 1.60, IQR 0.75-2.15) (p= 0.453).

At end of three month, all the 52 subjects were available for follow-up and biochemical estimations. The weight and length was significantly greater in Group 2 children who were given fortification in addition to the breast feed as compared to Group 1 children (weight 4.75±0.5 *vs* 3.40±0.3 kg; length 54.0±3.2 *vs* 50.4±2.5 cm). Daily weight gain was also significantly greater in Group 2 children (23.6±3.4 *vs* 17.0±4.6 g/day). Mean fasting glucose and insulin levels were also significantly greater in Group 2 as compared to Group 1 (glucose 85.6±8.4 *vs* 79.0±9.4 mg/dl; insulin (15.73±3.29 *vs* 6.95±4.27 µU/ml) (p<0.001). Non-parametric Mann-Whitney test also showed significant difference in median and IQR insulin values (Group 2: 15.05, IQR 13.38-17.93; Group 1: 6.50, IQR 3.17-10.50) (p<0.001). As the Group 2 children gained significantly more weight as compared to Group 1, weight adjusted fasting insulin levels were determined. The adjusted insulin levels were 11.26±3.3 µU/ml which were significantly greater than Group 1 (p<0.001).

Table 1. Baseline Clinical and Biochemical Characteristics in the Study Groups

Variable	Group 1 (n=26)	Group 2 (n=26)
Birthweight (kg)	1.99 ± 0.23	1.87 ± 0.30
Birth length (cm)	42.2 ± 2.4	42.8 ± 2.9
Head circumference (cm)	30.4 ± 1.8	29.9 ± 1.5
Chest circumference (cm)	28.2 ± 2.1	27.7 ± 1.8
Hemoglobin (g/dl)	16.0 ± 1.2	15.9 ± 1.4
Glucose fasting (mg/dl)	63.9 ± 9.8	64.3 ± 8.0
Insulin mean (µU/ml)	1.44 ± 1.19	1.73 ± 1.38
Insulin median and IQR (µU/ml)	1.10 (0.48-2.20)	1.60 (0.75-2.15)

IQR=interquartile range

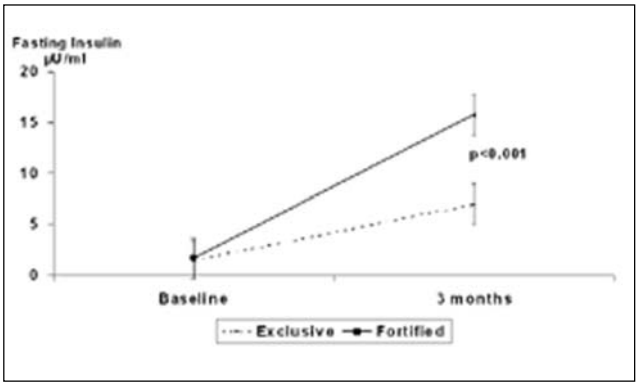

Fig. 2. Change in mean fasting insulin level in neonates with exclusive breast feeding as compared to fed fortified milk with breast feeding. At baseline, the mean insulin levels are similar in the two groups while at 3 months the fasting insulin levels are significantly greater in those breast fed with fortifier.

DISCUSSION

This study shows that early neonatal feeding practices influence weight gain and fasting insulin levels at three month age. Those fed fortified breast milk gained more weight and had greater fasting insulin and insulin

resistance compared to those with exclusive breast feeding. This difference persisted after the adjustment for weight. This shows that exclusive breast feeding and slow gain in weight is a better option in low birthweight children, to prevent early hyperinsulinemia which is a marker of insulin resistance.

A number of benefits have been attributed to exclusive breast feeding in the child and the mother.[16] Immediate advantages to the child include easy availability, no cost, hygiene, better digestibility, nutritive value, immunity to the infections, appropriate weight gain, infantile teeth development, and many psychological and neurodevelopmental benefits. It also prevents diarrhea, sudden infant death syndrome and childhood allergies. Long term benefits relate to better intelligence quotient, school performance and general health status in childhood and prevention from chronic diseases such as obesity, hypertension, obstructive sleep apnea, cancers of breast and colon, multiple sclerosis, rheumatoid arthritis, and type-1 as well as type-2 diabetes, in adulthood. It has been reported that breast feeding during the first three month of life is associated with a 34% decreased risk of diabetes.[3] The controversy is regarding the time of development of insulin resistance in the life cycle and effects of early intervention. This study shows that excessive feeding in the early months of the human lifecycle and rapid gain in weight is associated with insulin resistance, suggesting that insulin resistance is programmed in utero as a reaction to the maternal and fetal under nutrition and lead to development of a thrifty phenotype, as suggested by Barker[1] and others.[3,4] On the other hand, fortification is essential to maintain adequate childhood nutrition especially in undernourished mothers where the quantity and quality of milk may be inappropriate.

A Cochrane review to assess the effects of exclusive breast feeding,[17] reported that it is a better option compared to fortified feeding in preventing a number of acute or long term health issues related to growth and infections, but was not focused on the development of chronic diseases such as insulin resistance, diabetes or hypertension. The American Heart Association guidelines[18] on childhood nutrition to prevent adult diseases reviewed the studies on the relationship of breast-feeding to both future cardiovascular risk factors and cardiovascular events. It concluded that although pooling estimates from various studies is difficult because of differences in exposure and outcome assessment, meta-analyses suggested no meaningful impact of breast-feeding on subsequent cardiovascular or all-cause mortality in adulthood.[18] On the other hand, lower birth weight, because of presumed intrauterine malnutrition and association with rapid postnatal weight gain, has been associated with central adiposity, metabolic syndrome, diabetes mellitus, and cardiovascular disease outcomes in adulthood.[19] Many systematic reviews, however, suggest benefits of breast-feeding, particularly in the prevention of future obesity and diabetes.[20,21] Stettler *et al* studied the association between rapid weight gain and future obesity in American blacks and whites and reported that in formula fed infants rapid weight gain in the first wk of life is harbinger of obesity in childhood and young adulthood. In many studies, rapid weight gain during the first 4 to 6 month of life is associated with future risk of being overweight.[22,23] It is reported that partially breast-fed and formula-fed infants consume 20% more total calories per day than do exclusively breast-fed infants, which leads to childhood and later adult obesity.[24] The present study also shows that fortified feeding in early childhood is associated with more weight gain at 3 month of age associated with the presence of insulin resistance. Several studies suggest that breast-feeding leads to lower blood pressure later in childhood.[25] Although breast-feeding is associated with higher blood cholesterol levels at 1 yr of age, it may also result in lower blood cholesterol levels in adults.[26] We have not measured blood pressure or lipid levels and cannot comment on these issues.

Some groups have performed studies to evaluate effects of early infancy feeding practices on short and long-term development of insulin resistance and diabetes. Lucas and others studied influence of different feeding patterns on growth and insulin resistance in early childhood, in low birth neonates.[13] This study included two hundred eighty-four infants of which 229 were randomly assigned a protein, energy, mineral, and micronutrient-enriched formula (n=113) or standard term formula (n=116) after discharge. A reference group (n=65) was breastfed until at least 6 wks post-term. At 9 months, compared with the standard group, those fed enriched formula were heavier and longer. On the other hand at 6 wk exclusively breastfed infants were lighter and shorter than enriched diet group. These findings are similar to the present study. In a study that evaluated effects of fast early neonatal growth on insulin resistance, it was reported that adolescents born preterm who were randomized to a lower-nutrient diet, now recognized to be suboptimal in terms of growth, had lower fasting 32–33 split proinsulin concentrations and other markers of insulin resistance than those given a nutrient-enriched diet.[9] These dietary effects, seen up to 16 yr after dietary randomization, were probably the result of diet affecting the neonatal growth rate. It has been suggested that reduced early growth rate as a consequence of relative under nutrition, programs a lower insulin resistance and, by inference, a lower propensity to non-insulin-dependent diabetes mellitus.[4] The present study shows similar results inspite of limitations such as small sample size and limited follow-up, which are the limitations of this study. On the other hand, the findings of the present study have important message for the infant nutrition policies and support the guidelines of the pediatric

societies that recommend slow growth in undernourished children and recommend exclusive breast feeding in early months of life.

Contributions: MG planned and supervised the study, Zaheer and RJ collected data and carried out the study. RG and VK carried out analysis and critical evaluation.

Conflict of Interest: None.

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