Public Health Nutrition: 13(1), 4–11 doi:10.1017/S1368980009005886

Unexpectedly high early prevalence of anaemia in 6-month-old breast-fed infants in rural Bangladesh

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Submitted 21 July 2008: Accepted 4 March 2009: First published online 28 May 2009

Abstract

Objective: To determine the prevalence of anaemia and maternal and infant factors associated with Hb values in infants at 6 months of age in rural Bangladesh.
Design: Infants (born to mothers supplemented with Fe–folic acid from mid-pregnancy) were visited at birth and 6 months of age. Mothers' anthropometric status, and infants' birth weight, gestational age at birth, weight and Hb concentration at 6 months were measured. Household socio-economic and demographic data, infant feeding practices and health status were collected using a pre-tested structured questionnaire.
Setting: Rural Bangladesh.
Subjects: Four hundred and two infants.
Results: For the total cohort (n 402), the range of anaemia prevalence values was from 30·6% using a cut-off value of Hb < 95 g/l to 71·9% using a value of Hb < 110 g/l. Birth weight and month of birth were the only factors positively associated with infant Hb in a linear regression model ($P = 0{\cdot}008$ and 0·011, respectively).
Conclusions: There was an unexpectedly high prevalence of anaemia in infants at 6 months of age, before the assumed period of vulnerability. Hb at this age tended to be higher in those with higher birth weight. We also found a season effect on Hb, as it tended to be higher as the study progressed. The high prevalence of anaemia at such an early age needs to be addressed to minimize the disease's long-term consequences.

Keywords
Infancy
Anaemia
Bangladesh

Anaemia due to Fe deficiency remains the most common preventable nutritional deficiency in the world[1]. Anaemia has negative consequences in all age groups; in adults, it leads to fatigue and reduced work capacity, while in infants it is associated with compromised motor and mental function that may not be reversible[2,3]. The aetiology of Fe-deficiency anaemia in infants between 6 and 24 months of age is multi-factorial, including low content and bioavailability of Fe in unfortified complementary foods, depressed absorption of Fe due to chronic infection, rapid growth during this period and possibly early cord clamping[4–7]. Recommendations to introduce Fe-rich complementary foods after 6 months of age are partly based on the observation that in the full-term infant, it is expected that the combination of Fe stores at birth plus the minimal but highly bioavailable contribution from breast milk should suffice to meet the Fe needs of most infants up to 6 months of age[8]. It is after this time that infants are thought to be at risk of anaemia. In fact, daily Fe supplementation (12·5 mg of elemental Fe) is recommended for all infants between the ages of 6 and 24 months in areas where the prevalence of anaemia exceeds 40%[9].

Compared with infants in developed countries, it has been observed that anaemia may be prevalent at or before 6 months of age in infants in developing countries[10–12]. For example, high anaemia (defined as Hb < 110 g/l) prevalence was documented at 6 months of age in infants in Jordan and Israel (63% and 44%, respectively)[10,11]. Additionally, a 42% prevalence of anaemia has been documented in 4-month-old infants in a recent study in Benin[12]. Given the potential adverse effects of Fe-deficiency anaemia on infant development, from a public health perspective primary prevention would be preferable to screening and treatment. However, if anaemia onset is prior to 6 months of age, new recommendations for early prevention may be needed.

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Rates of poverty and malnutrition are high in rural Bangladesh[13], thus Bangladeshi infants are likely to be at high risk of early anaemia. To our knowledge, the prevalence of anaemia in infants at age 6 months has not been documented in this setting. Additionally, while it is known that birth weight is associated with Fe status in infancy, associations with other factors have not been clearly established[14–16]. Thus the objectives of the current study were to determine the prevalence of anaemia in Bangladeshi infants at 6 months of age and to identify maternal and infant factors associated with Hb concentration at this age. The study was largely exploratory. Nevertheless, we tentatively hypothesized that there would be a high prevalence of anaemia at this age and that both infant and maternal factors would contribute to Hb concentration at 6 months of age.

Methods

Setting

The study took place in Kaliganj, a rural sub-district in the Gazipur district of Bangladesh, 40 km north-east of Dhaka. Kaliganj is a fair representation of the geo-ecological attributes of the rural plains in Bangladesh, with high population density and fertile agricultural land that is vulnerable to seasonal floods[17]. Like most of rural Bangladesh, poverty and malnutrition are widespread in Kaliganj, and women and children bear the brunt of it[17]. There is still relatively limited access to health care and 75 % of women and 70 % of men do not have education beyond the elementary level[17]. The infant mortality rate and prevalence of low birth weight (LBW) are similar to the national averages for Bangladesh[18]. The study took place between March 2005 and April 2007 and was carried out as an academic collaboration between The Hospital for Sick Children, Toronto, Canada and the Research and Evaluation Division of BRAC (Building Resources Across the Community), Dhaka, Bangladesh.

Study design and participants

The study was a prospective cohort study whose sample consisted of 424 infants born to all of the mothers participating in a randomized, controlled, pregnancy supplementation trial comparing two groups of pregnant women receiving Fe and folic acid supplements delivered in the form of Sprinkles™ or tablets. In both treatment arms, from mid-pregnancy onwards, the women received daily supplementation containing the same amounts of elemental Fe (60 mg) and folic acid (400 μg). Thus, in the current study, infants from mothers in the two treatment groups were combined and treated as one cohort; however, all analyses controlled for the form of supplementation. The infants were visited at birth and then again at 6 months of age. Infants were included if their mother was a permanent resident in the study area, participated in the original study and provided informed consent. Infants were excluded if they had a birth defect or serious condition that required hospitalization, they were not singletons, they received Fe supplementation, infant mortality/stillbirth occurred, or if any of the inclusion criteria were not met.

Data collection

Mother's age, Hb, weight and height were measured at the mid-pregnancy recruitment visit (14 to 20 weeks' gestation; referred to henceforth as baseline). At this visit, gestational age was also calculated based on the last menstrual period (LMP) recall method[19]. At birth, the weight of the infant was measured and gestational age determined based on the calculation from the initial recruitment visit. At 6 months of age, the weight and Hb concentration of each infant were measured. At the same time, data on parity, child spacing, socio-economic status, feeding practices (prevalence and duration of exclusive breast-feeding (EBF)) and general health status were collected via a pre-tested questionnaire administered to the mother. EBF was defined as feeding/having been fed nothing other than breast milk. Data on general health were obtained by collecting information on immunization and prevalence of diarrhoea. One incidence of diarrhoea was defined as the passage of three or more loose/watery stools in a single day. Additionally, the mother's and interviewer's perception of the child's current state of health was collected. There is no consensus as to the anaemia cut-off at 6 months of age. While we present anaemia prevalence using several Hb cut-off values from the literature[20–22], the WHO definition of anaemia (Hb < 110 g/l) is taken as the standard for the purposes of the present study. For pregnant mothers, anaemia was defined as Hb < 110 g/l[21]. Severe anaemia was defined as Hb < 70 g/l[21]. Any child found to be anaemic (Hb < 110 g/l) at 6 months of age was referred to a BRAC community health worker or local health practitioner for Fe supplementation.

Hb was measured in the field from a finger-prick capillary blood sample using a portable HemoCue® β-Hemoglobin Photometer (HemoCue, Angelholm, Sweden). The CV of the photometer was 1·5 %. The technique is well established and was carried out as previously described by Meinzen-Derr *et al.*[23]. All weight measurements were completed using the UNISCALE (UNICEF Supply Division, Copenhagen, Denmark), which is accurate to 100 g, except for birth weight, which was measured using the hanging Salter-like scale (UNICEF Supply Division) that is accurate to 50 g. Both techniques have been described before[24].

Statistical analysis

All data forms were collected and checked for completeness before being entered into the storage database. Data were entered, stored and analysed using version

14·0 of the SPSS for Windows statistical software package (SPSS Inc., Chicago, IL, USA). The subject population and hence the sample size for the present study was derived from the original Fe–folic acid pregnancy supplementation study (the infants born to the 424 women). Nevertheless, in order to detect a prevalence of anaemia with 95 % confidence that was within 5 % of the true prevalence and assuming that the population of infants in Kaliganj was 6500[18], 363 infants would need to have been screened at 6 months of age. A one-sample Kolmogorov–Smirnov test was used to verify normality of the infants' Hb concentrations, the main outcome measure, and that of the other continuous variables collected; variables that were not normally distributed were log-transformed before analyses. Correlation matrices were generated to identify variables correlated with Hb concentration at 6 months of age. For continuous variables that were normally distributed, Pearson correlation values are presented, while for discrete, non-normal variables, Spearman's rho correlation coefficients are presented. To detect associations, linear regression analysis was performed with Hb and birth weight as dependent variables in separate models. A sub-analysis was performed on LBW infants to identify factors associated with Hb and anaemia in this group. In all analyses, statistical significance was defined as $P < 0·05$.

Table 1 Characteristics of mothers (*n* 402), Kaliganj sub-district, Bangladesh, March 2005 to April 2007

Characteristic	Mean	SD	Range
Household size	5·7	2·4	2, 17
No. of living children	1·8	1·1	1, 7
Total no. of conceptions*	2·1	1·3	1, 8
Average child spacing† (months)	51·1	22·6	17, 162
Time from last child‡ (months)	55·1	27·0	17, 162
Age at first pregnancy (years)	18·4	2·7	14, 32
Age§ (years)	22·2	5·0	14, 44
Total years of education	6·5	3·3	0, 14
Weight§ (kg)	46·4	7·0	28·3, 77·4
Height§ (cm)	150·2	5·5	132·1, 168·5
BMI§ (kg/m^2)	20·5	2·7	13·5, 34·2
Hb§ (g/l)	110·4	14·3	72, 150

*The total number of times the mother knew she was pregnant, regardless of outcome.
†For women with previous children; calculated by taking the difference between the eldest and youngest child and dividing by one less than the total number of children. Stillbirths and neonatal deaths were not taken into account in this calculation.
‡For women with previous children; calculated by taking the difference between the second youngest and youngest child.
§Measurement taken at 14–20 weeks' gestation; referred to as 'baseline'.

Ethics approval

The study protocol was approved by the Research Ethics Board at The Hospital for Sick Children (Toronto, Canada) and the Ethics Board of the Bangladesh Medical Research Council (Dhaka, Bangladesh).

Results

A summary of the maternal characteristics is presented in Table 1. Data were analysed for 402 mother–infant pairs. Twenty-two pairs were excluded from the analysis due to stillbirth (*n* 3), infant mortality (*n* 6), twin birth (*n* 1) or relocation (*n* 12) from the study area. This was the first child for 194 of the mothers in the study. Therefore, for the variables 'child spacing' and 'time since the last child', data are presented only for those with one or more previous children. At recruitment, 45·3 % (182/402) of the mothers were anaemic, but none had severe anaemia. Ninety-seven (24·1 %) mothers reported their perceived economic status as 'above average'.

Table 2 presents data on infant characteristics. There were 205 (51 %) male and 197 (49 %) female infants. For logistical reasons, we were unable to collect birth weight from 117 of the 402 infants. In infants with a known birth weight, the prevalence of LBW (<2·5 kg) was 36·1 % (103/285). Of these infants, 21·4 % (22/103) were born preterm (<37 weeks' gestation). At 6 months of age, of the 182 infants with normal birth weight, only nine (4·9 %) were significantly underweight (weight-for-age *Z*-score <–2), while thirty of the 103 LBW infants (29·1 %) were also significantly underweight; LBW infants were more likely to be underweight at 6 months of age (unadjusted OR = 7·9, 95 % CI 3·6, 17·5; $P = 0·000$). The prevalence of EBF at 6 months of age was only 1·7 % (7/402), while the mean duration of EBF was 70·3 d (SD 61·6 d, interquartile range 119 d). Most infants (98·5 %) had received at least one immunization. Fifty-seven infants (14·2 %) experienced at least one bout of diarrhoea in the last 7 d.

Given that there is disparity concerning the definition of anaemia at 6 months of age, Table 3 presents the

Table 2 Characteristics of infants born to mothers supplemented with Fe–folic acid from mid-pregnancy, Kaliganj sub-district, Bangladesh, March 2005 to April 2007

Characteristic	*n*	Mean	SD	Range
Actual date of birth relative to expected* (d)	402	3·1	19·5	−60, 45
Birth weight (kg)	285	2·8	0·4	1·3, 4·5
Weight at 6 months (kg)	402	6·9	0·9	4·5, 9·9
Growth rate (kg/month)	285	0·7	0·1	0·4, 1·1
Growth ratio relative to birth weight†	285	2·5	0·3	1·8, 4·0
Weight-for-age *Z*-score at 6 months of age‡	402	0·9	1·0	−4·1, 2·5

*Negative indicates earlier than expected. Expected date of birth determined based on recall of last menstrual period.
†Calculated by dividing the infant's weight at 6 months by his/her birth weight.
‡Based on the 2006 WHO growth charts.

Table 3 Prevalence of anaemia at 6 months of age based on the different cut-off values in the literature: infants born to mothers supplemented with Fe–folic acid from mid-pregnancy, Kaliganj sub-district, Bangladesh, March 2005 to April 2007

	Prevalence of anaemia			
	Total cohort of infants (n 402)		LBW infants (n 103)	
Anaemia cut-off value*	n	%	n	%
Hb < 95 g/l	123	30·6	29	28·2
Hb < 100 g/l	174	43·3	54	52·4
Hb < 105 g/l	221	55·0	74	72·8
Hb < 110 g/l	289	71·9	86	83·5

LBW, low birth weight.
*Cut-off values reported by Virtanen *et al.*[22], Domellof *et al.*[20] and WHO[21].

Table 4 Factors correlated with Hb concentration at 6 months of age among infants born to mothers supplemented with Fe–folic acid from mid-pregnancy, Kaliganj sub-district, Bangladesh, March 2005 to April 2007

Factor	Correlation coefficient	*P* value
Birth weight* (n 285)	0·209	0·000
Growth ratio (weight at 6 months/birth weight)* (n 285)	−0·195	0·001
Water feeding†,‡ (n 402)	0·116	0·023
Month of birth† (n 402)	0·209	0·000
Mother's age at first pregnancy† (n 402)	0·106	0·033
Teenage mother†,‡ (n 402)	0·111	0·026
Mother's baseline age† (n 402)	0·117	0·019
Mother's baseline BMI† (n 402)	0·104	0·037

*Pearson's r correlation coefficient.
†Spearman's ρ correlation coefficient.
‡Treated as a dichotomous variable (1 = yes, 2 = no).

prevalence of anaemia in the infants based on the different Hb cut-off values described in the literature. For the total cohort (n 402), the range of anaemia prevalence values was from 30·6 % using a cut-off value of Hb < 95 g/l to 71·9 % using a value of Hb < 110 g/l (the WHO definition of anaemia). For LBW infants (n 103), the range of anaemia prevalence was from 28·2 % to 83·5 % using the same cut-off values. Four infants (1 %) were severely anaemic. The mean Hb was 102·3 g/l (SD 12·4 g/l, range 64–134 g/l). Table 4 summarizes factors significantly correlated with Hb. The following notable variables were not correlated with the infants' Hb at 6 months: weight gain from birth to 6 months ($r = -0.041$; $P = 0.486$), gestational age at birth ($r = 0.08$; $P = 0.114$), duration of EBF ($r = 0.022$; $P = 0.664$), mother's baseline age ($r = 0.08$; $P = 0.108$), mother's weight ($r = 0.076$; $P = 0.128$), mother's height ($r = 0.009$; $P = 0.853$) and mother's Hb ($r = 0.07$; $P = 0.161$). Additionally, none of the infant health indices were correlated with Hb at 6 months. After adjusting for infant gender, the birth of previous children, duration of gestation, mother's treatment group and mother's baseline Hb, the only significant predictors in the linear regression model (model $R^2 = 10.4$ %; $P = 0.000$) of Hb at 6 months of age were infant birth weight (standardized $\beta = 0.214$; $P = 0.000$) and month of birth (standardized $\beta = 0.171$; $P = 0.011$; Table 5). Removing LBW infants from the analysis did not alter the significance of any factor.

Table 5 General linear model* with infant Hb concentration at 6 months of age as the response variable

Predictor variable	Standardized β	*t* statistic	*P* value
Birth weight	0·214	3·23	0·000
Month of birth	0·171	2·83	0·011
Infant gender†	0·044	0·75	0·46
First pregnancy‡	−0·034	−0·58	0·57
Duration of gestation	−0·042	−0·67	0·50
Mother's baseline Hb	0·039	0·65	0·52
Mother's treatment group	−0·001	−0·014	0·99

*Model's adjusted R^2 = 10·4 % (P = 0·000).
†Male = 1, female = 2.
‡Treated as a dichotomous variable (1 = yes, 2 = no).

For LBW infants, stepwise linear regression analysis (forward; P value for retention <0·05) revealed that absolute weight gain from birth to 6 months (negatively associated; standardized $\beta = -0.42$; model $R^2 = 17.6$ %; $P = 0.001$) was the only significant predictor of Hb at 6 months of age.

Discussion

The high prevalence of anaemia in infants at 6 months of age born to Fe-supplemented mothers in the present study highlights a significant health problem in rural Bangladesh. The most vulnerable period for Fe deficiency and anaemia in full-term infants is between 6 and 24 months, and Hb is

https://doi.org/10.1017/S1368980009005886 Published online by Cambridge University Press

thought to reach its minimum at 9 months of age[25]. It is during this period that blanket Fe supplementation programmes are recommended in populations with a known prevalence of anaemia (defined as Hb < 110 g/l) of over 40 %[21]. However, in the present study, over 70 % of infants would be classified as anaemic based on this cut-off value. Even with a more conservative anaemia cut-off (Hb < 105 g/l), 55 % of infants were already anaemic even by 6 months of age. Thus, these infants are already exposed to the negative consequences of anaemia before they enter this known period of vulnerability. In developed countries, Fe supplementation is only recommended before 6 months of age for LBW infants, and even then adherence to this recommendation is low[23,26]. However, there are no strategies for Fe supplementation of LBW infants in developing countries other than EBF.

There is some debate as to the anaemia cut-off value at 6 months of age[20–22]. Therefore, we present anaemia prevalence based on various proposed cut-off values (Table 3). The prevalence of anaemia based on the WHO cut-off of Hb < 110 g/l is alarmingly high (71·9 %), almost double that required for the WHO's blanket Fe supplementation recommendations. Nevertheless, using the most conservative cut-off (Hb < 95 g/l), nearly one-third of infants would still be classified as anaemic. At the cut-off suggested by Domellof *et al.*[20], in which they report 105 g/l as the mean minus two standard deviations in a cohort of Fe-replete infants, more than half of infants at age 6 months would be classified as anaemic in the present study. However, until there is scientific agreement on a new standard, we continue to use the WHO cut-off for anaemia at this age.

After controlling for confounding variables, birth weight and month of birth were the only infant factors significantly associated (both positively) with Hb concentration at 6 months of age. This confirms previous findings which document the impact of birth weight on body Fe stores and Hb concentration[14–16]. Babies with LBW, whether because of prematurity or because they are small for gestational age, have lower Fe stores. Thus it makes sense that they will become Fe-depleted at an earlier age. The observed association between Hb and birth month is somewhat hard to explain but may be attributed to environmental effects. Infants in the current study were born between January and September 2006. Therefore, the 6-month Hb measurement took place between July 2006 and March 2007. As the months progressed, there was a trend toward increasing Hb among the infants. In rural Bangladesh, January, February and March are post-harvest months. During these months there is an abundance of inexpensive fruits available to all. As a result, the vitamin C consumption in these infants, the majority of whom were not exclusively breastfed, was likely higher, possibly leading to higher Fe absorption. Alternatively, the earlier months of Hb measurement (July, August and September) are during the monsoon season, when rates of infection are likely higher. However, it must be noted that the prevalence of anaemia (defined as Hb < 110 g/l) was still over 44·7 % (51/114) in the latter months of the study. Seasonal variation in anaemia prevalence has not been well documented in children; however, among pregnant Nepali women, variation in anaemia rates was attributed to limitations in availability of food along with increased intestinal infections during the Nepali monsoon season[27]. In infants born in malaria-endemic areas of Africa, seasonal variation in anaemia has been attributed to malaria[28,29]. However, malaria prevalence is low in Kaliganj and not likely a contributor[17].

Absolute weight gain was not associated with Hb concentration at 6 months in the entire cohort of infants but was negatively associated with Hb in LBW infants. It has been previously documented that weight gain is negatively associated with Fe status in infancy[14,15,30,31]. Blood volume and weight gain are thought to be linearly associated in infancy, as infants typically triple both their weight and their blood volume in the first year of life[32]. Consequently, the more rapid the weight gain, the greater is the need for Fe to keep up with the rapid expansion of the blood volume. This in turn should translate into a lower Hb concentration. We did not measure serum ferritin concentration in our study, and thus are unable to comment on an association between weight gain and Fe stores. Although Fe status was not measured, we assume that the primary cause of anaemia was Fe deficiency since the typical complementary foods used in rural Bangladesh are low in bioavailable Fe and not fortified, and animal-based foods rich in Fe are rarely provided to infants[33].

We did not find an association between duration of EBF and Hb at 6 months of age; however, the duration of EBF was very short among a large proportion of mothers in this cohort and the prevalence of EBF at 6 months of age was very low. This resulted in a highly skewed distribution of duration of EBF, and therefore an insufficient number of mothers who practised EBF into the fifth and sixth months. It has been previously reported that the prevalence of EBF at 6 months of age is 29 % across Bangladesh[34]. However, Roy *et al.* found a 7·7 % prevalence of EBF at 6 months in the capital city, Dhaka[35]. We expected that the prevalence of EBF would be much higher in the rural areas, especially since there is very limited access to breast milk substitutes, but this was not the case in our study. Not only would EBF benefit the infants in terms of the provision of passive immune factors and good nutrition, but EBF up to 6 months of age has been shown to impact positively on Hb status at 6 months of age[36,37]. However, given the feeding practices in our population, we were unable to detect any associations. The high prevalence of low EBF rates has been well documented in the past, leading to the implementation of a national programme in 1989 entitled the 'Campaign for Protection and Promotion of Breastfeeding

(CPPBF)'[38]. This programme, now termed the BBF (Bangladesh Breastfeeding Foundation), aims to 'counter the delayed initiation of breastfeeding, administration of pre-lacteal foods, early complementary feeding, bottle feeding, and the very low rates of exclusive breastfeeding'[38]. However, the programme, although implemented almost 20 years ago in Bangladesh, has yet to reach the sub-district of the present study's setting and many others in rural Bangladesh (F Haseen, personal communication).

As previously noted, there were no maternal factors significantly associated with Hb in the infants at age 6 months in the controlled linear regression model. In a previous study on 990 infants in rural Indonesia[39], the authors found that 3- to 5-month-old infants born to anaemic mothers had significantly lower Hb concentrations than infants born to non-anaemic mothers. However, the authors did not specify at what point during the pregnancy Hb was measured in the mothers. The relationship between maternal haematological status during pregnancy and that of her infant has long been controversial, with some studies suggesting no association[40–42] while others report a positive relationship[43–45]. It is feasible that Hb status in pregnancy would impact on anaemia prevalence in infants. Over 50 % of maternal anaemia in the world is due to Fe deficiency[46]. The placenta is rich in transferrin receptors thus facilitating the transfer of Fe from the maternal to the fetal side of the placenta, often at the expense of the mother[47]. However, if the mother is severely Fe-depleted, it is highly likely that the net transfer of Fe will be affected[48]. On the other hand, the fact that no association was observed between infant and maternal Hb in the current study more than likely reflects the fact that none of the mothers was severely anaemic.

There is a growing body of literature implicating the timing of cord clamping as an important factor influencing the Fe endowment of the infant, as it determines the amount of placental blood (and consequently Fe) transferred to the child after birth. The authors of a meta-analysis of fifteen studies on cord clamping and Fe status concluded that cord clamping should be delayed for at least 2 min after birth to improve the Fe status of the newborn[49]. However, the general practice among traditional birth attendants in Bangladesh is to clamp the cord immediately after birth[50]. Unfortunately, data on the timing of umbilical cord clamping were not collected in the current study due to the complex logistics associated with home childbirth in a rural setting. Nevertheless, given the traditional practice in Bangladesh of early clamping, it is quite likely that this is a contributing factor to the high prevalence of early anaemia.

Conclusion

The high prevalence of anaemia in 6-month-old infants in rural Bangladesh is a serious public health problem, especially among LBW infants. To date, strategies to reduce anaemia prevalence have not been successful. Anaemic infants entering the vulnerable period for Fe-deficiency anaemia (6–24 months of age) have already been exposed and are likely to be further exposed to the negative consequences of anaemia. While birth weight is known to be associated with anaemia, there has been minimal success at lowering the prevalence of LBW in Bangladesh. Given the findings of the current study, there is a need for further research to understand the factors predisposing infants to early anaemia, and to examine why programmes to increase birth weight have not been successful.

Acknowledgements

The authors acknowledge the following sources of funding: (i) Y.A.S. was supported in part through a studentship by the Ontario Student Opportunity Trust Fund, The Hospital for Sick Children Foundation Student Scholarship Program; (ii) Y.A.S. was also supported through a Canada Graduate Scholarship Master's Award, Canadian Institutes of Health Research (CIHR), FRN 81770; and (iii) an H.J. Heinz Foundation Research Grant. There are no real or perceived potential conflicts of interest associated with the work. The first draft of the manuscript was written by the first author, Y.A.S. All authors were involved in study design and editing of the manuscript. Y.A.S. and N.C. planned and executed data collection. Y.A.S. and S.M.Z.H. performed the statistical analyses. S.H.Z. oversaw the entire study. We gratefully thank Mr Mizanur Rahman for his help in the translation involved with this work.

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