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Early prenatal food supplementation ameliorates the negative association of maternal stress with birth size in a randomized trial

Amy L. Frith[*], **Ruchira T. Naved**[†], **Lars Ake Persson**[‡], and **Edward A. Frongillo**[§]

[*] Ithaca College, School of Health Sciences and Human Performance, Ithaca, New York 14850

[†] International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh

[‡]Uppsala University, Women's and Children's Health, International Maternal and Child Health, 751 85 Uppsala, Sweden

[§]University of South Carolina, Department of Health Promotion, Education, and Behavior, Columbia, SC 29208

Abstract

Low birth weight increases the risk of infant mortality, morbidity, and poor development. Maternal nutrition and stress influence birth size, but their combined effect is not known. We hypothesized that an early invitation time to start a prenatal food supplementation program could reduce the negative influence of prenatal maternal stress on birth size, and that effect would differ by infant sex. A cohort of 1041 pregnant women, who had delivered an infant, June 2003-March 2004, was sampled from among 3267 in the randomized controlled trial, Maternal Infant Nutritional Interventions Matlab, conducted in Matlab, Bangladesh. At 8 wk gestation, women were randomly assigned an invitation to start food supplements (2.5 MJ/d; 6 d/wk) either early (~9 wk gestation; early-invitation group) or at usual start time for the governmental program (~20 wk gestation; usual-invitation group). Morning concentration of cortisol was measured from 1 saliva sample/woman at 28-32 wk gestation to assess stress. Birth size measurements for 90% of infants were collected within 4 d of birth. In a general linear model, there was an interaction between invitation time to start the food supplementation program and cortisol with birth weight, length, and head circumference of male infants, but not female infants. Among the usual-invitation group only, male infants whose mothers had higher prenatal cortisol weighed less than those whose mothers had lower prenatal cortisol. Prenatal food supplementation programs that begin first trimester may support greater birth size of male infants despite high maternal stress where low birth weight is a public health concern.

Address for correspondence: Amy Frith, Ithaca College, School of Health Sciences and Human Performance, 953 Danby Rd., Ithaca, New York 14850; telephone: 607-274-5135; facsimile: 607-274-1174; afrith@ithaca.edu.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Keywords

Maternal Nutrition; Stress; Low Birth Weight; Prenatal Food Supplement; Low Income Countries; Gestational Age

Introduction

Improving birth weight to reduce infant mortality and morbidity is a priority worldwide (Black *et al.* 2008), particularly in Asia where ~30% of infants are born with low birth weight (LBW) (UNICEF 2009). Fetal growth restriction that leads to LBW is associated with adverse neurodevelopmental outcomes (Geva *et al.* 2006, Many *et al.* 2005), lower intelligence quotient (Many *et al.* 2005), reduced immunocompetence (Raqib *et al.* 2007), increased risk of chronic diseases (Grigore *et al.* 2008, Martin-Gronert & Ozanne 2007, Hales & Barker 2001), and reduced human capital (Victora *et al.* 2008). Prenatal stress and depression are associated with reduced birth size (Dunkel-Schetter 2011, Diego *et al.* 2009, 2006, Field *et al.* 2008, Rini *et al.* 1999, Valladares *et al.* 2009). In low- and middle-income countries, many women suffer from not only high stress and depression (Nasreen *et al.* 2010, Rahman *et al.* 2007), but also poor diets, leading to inadequate weight gain during pregnancy, that also contributes to LBW (Kramer 1987, Hosain *et al.* 2006). The combined influence of prenatal maternal nutrition and stress on birth size is not known, but is important to understand to develop effective interventions to prevent LBW.

Wadhwa and colleagues proposed a biopsychosocial model whereby greater prenatal stress reduces birth weight through neuroendocrine, immune and cardiovascular systems (Wadhwa *et al.* 1996). Prenatal stress increases the activity of the hypothalamic-pituitary-adrenal axis (Dunkel-Schetter 2011, Field *et al.* 2008), thereby, elevating maternal cortisol (Diego *et al.* 2009) and reducing birth weight (Deigo *et al.*, 2006, Field *et al.* 2008) either through reducing uterine blood flow and nutrient delivery to the fetus (Vythilingum *et al.* 2010, Texeira *et al.* 1999) or by direct effects on the fetus (Diego *et al.* 2009). Poor maternal nutritional status may further increase the exposure of the fetus to cortisol by reducing the enzyme 11β-hydroxysteroid dehydrogenase in the placenta (Lesage *et al.* 2001, Shams *et al.* 1998, Langley-Evans *et al.* 1996). This enzyme converts maternal cortisol to cortisone and protects the fetus from maternal cortisol (Benediktsson *et al.* 1997). In one observational study, prenatal maternal stress was associated with birth weight only in the infants of less well-nourished women (Cliver *et al.* 1992).

Prenatal food supplementation programs provide food containing nutrients that can prevent fetal growth restriction in populations that suffer from a high prevalence of LBW (Hoynes *et al.* 2011, Bhutta *et al.* 2008, Khatun & Rahman 2008, Osrin *et al.* 2005, Bitler & Currie 2005). In general the more food supplement consumed or the longer the participation in the program (beginning in the second rather than third trimester) the larger the infant at birth, yet the effects of prenatal food interventions on birth size have been mixed (Gueorguieva *et al.* 2009, Shaheen *et al.* 2006, Bitler & Currie 2005, Winkvist *et al.* 1998, Kardjati *et al.* 1988, Mora *et al.* 1979, Lechtig *et al.* 1975). The effect of these programs may depend on amount and composition and timing of supplements, maternal nutrition status, seasonal

variation, stress, and sex of the infant that influence either fetal growth, maternal nutritional status, or both (Lampl *et al.* 2010, Clifton 2010, Shaheen *et al.* 2006, Bitler & Currie 2005, Winkvist *et al.* 1998, Mora *et al.* 1979). There are sex-differentials in fetal growth or birth weight that are influenced by maternal nutritional status (Lampl *et al.* 2010), insults (Clifton 2010), and prenatal nutritional supplementation (Osrin *et al.* 2005).

Given that both stress and food supplementation may influence birth size, we examined the combined influence of two different times to invite pregnant women to start a prenatal food supplementation program (early-invitation group, ~ 9 wk gestation; or usual-invitation group, ~ 20 wk gestation) and prenatal maternal stress (i.e., concentration of cortisol) on birth size in a cohort of pregnant women in rural Bangladesh. In the early-invitation group, pregnant women received more food overall and earlier in pregnancy than the usual-invitation group. We hypothesized that mothers with high prenatal stress (i.e., high concentration of cortisol) would have smaller infants compared to mothers with low prenatal stress (i.e., low concentration of cortisol) in the usual-invitation group, but not in the early-invitation group, and furthermore this effect would differ by sex of the infant.

Subjects and Methods

Study design

This study was conducted between June 2003 and March 2004 in Matlab, a subdistrict of the Chandpur district that is typical of the rural and riverine delta of Bangladesh (van Ginneken *et al.* 1998), by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). Written informed consent was obtained from each woman before enrollment. The institutional review boards of ICDDR, B and Cornell University approved the study protocol.

This study was part of a larger study, Maternal and Infant Nutritional Interventions, Matlab (MINIMat) (Persson *et al.* 2012), registered as an International Standard Randomized Controlled Trial, number ISRCTN16581394. The primary objective of the MINIMat study was to determine the influence of nutritional interventions on infant mortality, birth weight, and maternal hemoglobin. MINIMat was a randomized controlled field trial with a 2 × 3 × 2 factorial design. All pregnant women at 8 wk of gestation were randomly and independently assigned to receive 1 of each of the 3 nutritional interventions. Each participant was assigned to a food supplementation group, either invitation and promotion to “early” start of daily food supplementation (2.5 MJ/d; 6 d/wk) (~ 9 wk of gestation) or to no such invitation and promotion, which is “usual” start of participation in the governmental program (~ 20 wk of gestation) until birth. Each participant was also assigned to receive 1 of 2 counseling protocols from 30 wk of gestation until 6 mo after giving birth as follows: either usual health messages alone (UHM) or usual health messages with exclusive breastfeeding counseling (EBC). Beginning at 14 wk of gestation until 3 mo postpartum, each participant received 1 of 3 daily micronutrient supplements of either 60 mg or 30 mg of iron with 400 μg folic acid or multiple micronutrients (30 mg iron with the UNICEF formulation) (Frith *et al.* 2009).

The sample for this sub-study was recruited from all eligible MINIMat participants who gave birth between June 2003 until March 2004. Of the 1300 pregnant women that were

recruited, we collected cortisol from 1041. One hundred and thirteen women had temporarily moved to another location outside of Matlab for the pregnancy and birth; 11 had permanently moved; 20 were absent from their homes and no one reported where they had gone; 2 women refused to participate; 2 women had measles; and 111 had either miscarried, dropped out of the MINIMat study, or were pregnant with twins.

Maternal characteristics

Maternal characteristics including parity, age, and wealth index during early pregnancy were assessed by questionnaire at 8 to 10 wk of gestation. A wealth index was used to assess socioeconomic status based on a composite of information about land ownership, characteristics of the household dwelling, and household ownership of durables (i.e., bed, quilt, mattress, watch/clock, chair/table, cabinet, bicycle, radio, television, electric fan, cows, goats, chicken/ducks) (Gwatkin *et al.* 2000). Maternal height and weight were measured at 8 to 10 wk of gestation.

Food supplement

Pregnant women received and consumed the food supplement that was supplied as individual packets daily for 6 d/wk by a community nutrition educator at a community nutrition center from the assigned invitation to start time (i.e., early or usual) until 8 mo of gestation. The community nutrition educators were local women who were trained by the implementing organization, BRAC, to deliver nutrition education messages and to encourage women to consume food packets completely on site. From 8 mo of gestation until birth, food supplement was delivered to participant's homes. The composition of the food supplement was in accordance with the US recommended daily allowance and international recommendations (Institute of Medicine 1999, National Research Council 1989), and the supplement was intended as a snack to supplement, not to replace, home food consumption. The supplement contained rice, lentils, molasses, and oil, and contained 2.5 MJ/d 6 d/wk (29% of recommended energy intake), 25% of which was vegetable protein. The consistency was culturally acceptable as it was based on a common type of food. In the main MINIMat study, the early-invitation group began consumption approximately 2.5 mo earlier and, on average, consumed more supplement packets over the course of the pregnancy (105 packets) than the usual-invitation group (66 packets). In this sub-study, the early-invitation group consumed more packets than the usual-invitation group (86 ± 49 and 57 ± 41, respectively; $p<0.05$). The difference in packet consumption between the main study and sub-study is most likely due to differences in flooding severity during the 3 years of the main study and the 1 year of the sub-study (Shaheen *et al.* 2006).

Prenatal salivary cortisol

Morning cortisol was used as a biomarker of stress with higher concentrations indicating more stress (Steptoe *et al.* 2000, Pruessner *et al.* 1997) as demonstrated in pregnant women (de Weerth & Buitelaar 2005). Concentrations of cortisol are low at awakening, rise to a peak about 30 minutes after awakening, and fall towards baseline concentrations throughout the morning and afternoon (Pruessner *et al.* 1997). The average concentration of cortisol during this "awakening response" is associated with the person's overall exposure of cortisol

during the day, and increased concentrations are associated with more chronic and acute stress (Steptoe *et al.* 2000).

We measured cortisol from 28-32 wk of gestation because, in a previous study, maternal stress at this time of gestation was associated with poor birth outcomes (Copper & Goldenberg 1996). Community field workers visited the participant's homes and collected 1 saliva sample from each participant between 7 and 8 am using a salivette (Sarstedt Canada, Inc., St. Laurent, Quebec). These morning samples measured the awakening response as they approximated 30 minute to 1 h post-awakening samples, and were highly correlated to morning awakening concentrations of cortisol as determined in a pilot study. In the pilot study we conducted in Matlab, 3 morning saliva samples were collected, at awakening, 30 minutes to 1 hour post-awakening, and 3 hours post-awakening, from 27 pregnant women (25-30 wk gestation) to ascertain the pattern of awakening response of cortisol, and to decide if 1 morning sample could distinguish those with lower from those with higher awakening responses of cortisol. Concentration of cortisol collected between 7 and 8 am were correlated ($r = 0.75$; $p < 0.01$) with entire area under the curve of the awakening response of cortisol so that one sample per participant could assess whether a mother had a lower or higher concentration of cortisol. The mean concentration of cortisol from between 7 and 8 am was similar to mean concentrations reported in published studies that collected samples from pregnant women approximately 1-3 hours after awakening (de Weerth & Buitelaar 2005).

Participants were given a cylindrical cotton swab, chewed on it for 30-45 s or until it was fully saturated, and placed it in a test tube with cap. Samples were collected daily, frozen, and stored at −20°C on the same day. Samples were processed later and were centrifuged for 10 min, 1000 × g at 4°C to collect saliva. Concentration of cortisol was measured by a solid-phase ^{125} I radioimmunoassay (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA) by the laboratory of Dirk Hellhammer, University of Trier, Trier, Germany. The assay sensitivity was 1.0 nmol/l. The inter-assay variability was 4.5%, and the intra-assay variation was 3.0%.

Infant characteristics

Trained health workers measured and collected information on infant birth characteristics, including sex, birth weight (g), birth length (cm), and head circumference (cm) in 79.5% of infants within 1 d of birth, and in 90% of infants within 4 d of birth. The other infants in the analysis had their first weight taken within 30 d after birth. Birth-size measurements taken during the first 24 hr were used without adjustments. Measurements taken from 24 hr to 30 d after birth were adjusted using a standard deviation score transformation with the assumption that infants tend to remain relatively positioned in the anthropometric distribution during this time period (Arifeen *et al.* 2000). The last menstrual period (LMP) date was used for the calculation of gestational age. When the community health research worker (CHRW) of ICDDR,B visited the participant each month, the CHRW asked the participant when her last menstrual period occurred. If a woman reported to that her LMP was overdue or that she was pregnant, she was offered a pregnancy test (ACON, San Diego, California) and the date of her LMP was recorded.

Data analysis

Data were recorded in the field on pretested forms and were checked by the supervisor before and after the data were entered into computers. Analyses were done by SPSS software (version 18; SPSS Inc., Chicago, IL). Univariate analysis was used to identify outliers, which were then checked against the original filed forms and resolved. We used the birth measures as the primary outcomes measures for evaluating the influence of maternal prenatal stress and invitation time to start the food supplement program on infant outcomes.

Each participant received one type of food, counseling, and micronutrient intervention. For this study, the types of counseling and micronutrient supplementation were ignored after we established that these interventions did not modify the relationship of cortisol on birth weight, length, or head circumference; for example, using analysis of variance, we found that interaction terms were not significant (p-interaction > 0.10) for cortisol and types of counseling or cortisol and types of micronutrient supplement on birth weights of all, female, or male infants. The distribution of the sample among micronutrient and counseling groups was equivalent across food supplement groups. We used a *t* test for continuous variables and a *chi-square* test for categorical variables to determine the following: 1) whether characteristics of participants in this study differed from the larger MINIMat trial; 2) whether values of demographic and anthropometry characteristics and food-supplement intake differed between those who participated in the study and those who did not; and 3) whether prenatal maternal or infant characteristics differed by invitation time to start food supplementation, concentration of maternal cortisol (i.e., stress), or sex of the infant.

To test our study hypothesis that the invitation time to start the prenatal food supplementation modifies the relationship of prenatal maternal stress (i.e., concentration of cortisol) with birth size (i.e., birth weight, length, and head circumference), we used a general linear model that included concentration of cortisol, invitation time to start the prenatal food supplementation groups, and the interaction between them, controlling for the design variable for type of micronutrient supplement. The models were conducted separately for each sex, because previous studies have shown sex-differentials in fetal growth or birth weight (Lampl *et al.* 2010, Clifton 2010) including with prenatal nutritional supplementation (Osrin *et al.* 2005). Concentration of cortisol was a continuous variable in the general linear model for all birth measures; a categorical variable for cortisol (i.e., above and below median concentration of cortisol 9.6nmol/l) was used to examine the difference in birth weight between those with higher and lower cortisol. Concentrations of cortisol were normally distributed so they are reported as means ± SDs. Birth measures are reported as means ± SDs. We reported 2-sided p-values; a p-value of 0.05 was considered significant.

We also tested for potential confounders, i.e., maternal BMI, age, wealth, and parity (either as a continuous or a bivariate variable), and found that the relationship of food supplementation and cortisol with birth size was the same as when these variables were not added to the model. Timing of food supplementation did not interact with maternal covariates (i.e., BMI, age, wealth and parity) to influence birth size, nor were there significant 3-way interactions of timing of food supplementation, cortisol, and maternal covariates to influence birth size.

Results

Demographic and anthropometric characteristics and concentrations of cortisol of the 1041 pregnant women did not differ significantly or substantively between the food supplementation groups or from those who had male or female infants **(Table 1)**. Pregnant women who had high cortisol (i.e., cortisol > median value of 9.6 nmol/l) had lower body mass index, were younger, and had fewer children than women with low cortisol (i.e., cortisol ≤ median of 9.6 nmol/l), but wealth index did not differ significantly or substantively. There were no significant or substantive differences in maternal characteristics between those who participated in this study and those who had moved or decided not to participate (data not shown).

Infant birth weight, length, head circumference, percentage of LBW, and gestational age did not significantly or substantively differ between the food supplementation groups **(Table 2)**. Mothers with higher cortisol had infants with lower birth weights ($p<0.01$), smaller head circumferences ($p<0.01$), reduced age at gestation ($p<0.01$), and a tendency to have shorter length at birth ($p=0.08$) (Table 2). Overall, female infants had lower birth weights ($p=0.01$), smaller head circumferences ($p<0.01$), shorter length at birth ($p<0.01$), and higher percentage of LBW ($p=0.03$) than males. The percentage of female infants did not differ significantly or substantively between food supplementation groups or between those whose mothers had low or high cortisol.

For male infants, the relationship of maternal cortisol and birth weight and head circumference differed by invitation time to start the food supplementation, and there was a trend for an interaction for birth length **(Table 3)**. In the usual-invitation group, higher cortisol was associated with lower birth weight, and head circumference, with a trend for lower length. In contrast, in the early-invitation group, cortisol was not associated with birth weight, length, and head circumference. For example, for birth weight, the slope in the usual-invitation group was −20.1 g per nmol/l of cortisol, whereas the slope in the early-invitation group was close to zero (5.2 g per nmol/l = 25.3-20.1). In the usual-invitation group, given the standard deviation of cortisol of 3.5 nmol/l, the slope of 20.1 g per nmol/l represents a difference of about 280 g in birth weight across the range of cortisol in the sample; this means that women in the usual-invitation group with very high concentrations of cortisol would have much lighter male infants than women with very low concentrations of cortisol. For the usual-invitation group, when cortisol was categorized by > or ≤ the median value, there was a 148 g difference in birth weight of males (g; means ± SEM; 2672.5 ± 38.5 and 2820.2 ± 34.9, respectively).

For female infants, the relationship of maternal cortisol and birth size did not differ significantly or substantively by invitation time to start the food supplementation **(Table 4)**. Furthermore, cortisol was not associated with birth weight, length, and head circumference in either the usual- or early-invitation group.

We tested for the possibility that gestational age mediated the relationships among invitation time to start the food program, cortisol, and birth size by controlling for gestational age in the models with the three birth-size variables and the interactive term between food group

and cortisol. Gestational age did not attenuate the relationship of food group and cortisol on birth size for all infants or for males infants only (data not shown). Gestational age did not differ between male and female infants (Table 1). Cortisol was related negatively with gestational age in both males ($\beta = -0.06$; $p<0.01$) and females ($\beta = -0.04$; $p=0.05$).

Discussion

Early invitation to a prenatal food supplementation program ameliorated the negative association of prenatal salivary cortisol, a biomarker for stress, on birth size of male, but not female infants in a randomized controlled field trial. In the usual-invitation group, higher maternal cortisol (i.e., higher maternal stress) was associated with reduced birth size of male infants. This relationship was not observed for female infants.

Pregnant women with higher prenatal cortisol and in the usual-invitation group had male infants that were 148 g lighter on average than those in with lower level of prenatal cortisol. The magnitude of this effect on birth weight is biologically important as an increase of 100 g in mean birth weight is associated with a 30–50% reduction in neonatal mortality (Shrimpton 2003). In our study, every woman was part of the food supplementation program, so the influence of prenatal cortisol (i.e., stress) on LBW when there is no food intervention may be even greater than reported here. The reduction in birth weight for male infants in this study is comparable to that reported in observational studies where maternal depression reduced birth weight by 300 g in the US (Field *et al.* 2008) and 100 g in Bangladesh (Nasreen *et al.* 2010). The large effect of depression on birth weight in the US is comparable to the difference due to higher altitudes (Haas *et al.* 1980), and may be, in part, a function of the 20% higher average birth weight in the US compared to Bangladesh. Furthermore, women in Bangladesh are more likely than women in the US to have low pre-pregnancy body mass index and poor energy intake during pregnancy (Shaheen & Lindholm 2006, Alam *et al.* 2003, Kramer 1987). Poor maternal nutrition may limit birth weight to the extent that stress may not have as much influence on birth weight in this study population (Asling-Monemi *et al.* 2009) as in the US.

Mechanisms

The mechanisms whereby stress influences birth outcomes may be biological and social. Higher prenatal stress increases maternal concentration of cortisol that could reduce fetal growth through reducing uterine blood flow and nutrient delivery to the fetus, or may influence fetal growth directly (Dunkel-Schetter 2011, Vythilingum *et al.* 2010). In the early-invitation group, high maternal stress was not associated with reduced fetal growth in males. Mothers in the early-invitation group consumed an average of 30 more food packets, and began consuming them earlier (starting at approximately 9 wk instead of 20 wk of gestation), thereby, potentially increasing the nutrients available for early fetal growth. This may be important as early growth restriction that has been detected as early as 8 wk gestation (Smith *et al.* 1998).

Early food supplementation may also promote a healthier placental environment for fetal growth (Magnusson *et al.* 2004, Clarke *et al.* 1998). In an observational study in Bangladesh, earlier start of and longer participation in a food supplement program

(beginning in second trimester) was associated with heavier infants at birth (Shaheen *et al.* 2006). In sheep, greater energy consumption during early and mid-gestation increases placental size, which is associated with increased birth weight (Clarke *et al.* 1998). Christian (2010) in a recent review outlined several pathways whereby maternal nutrition early in pregnancy could plausibly influence fetal growth and development. In early pregnancy, an increase in maternal plasma volume is necessary to deliver nutrients and oxygen to the developing fetus. Women who are underweight have a higher risk of having inadequate plasma volume leading to poor fetal growth (Rosso *et al*. 1992). Early food supplementation may improve plasma volume resulting in better fetal growth. Another process that occurs early in gestation and may be influenced by maternal nutrition is placental function and development. If early supplementation improves placental weight or vascularization, then nutrient and oxygen delivery to the fetus could increase resulting in increased fetal growth. A study in India reported that mothers who consumed more nutrient-dense foods had heavier placentas (Rao *et al*. 2001). Furthermore, in animals and humans with fetal growth restriction, the placentas of poorly nourished females have less ability to convert maternal cortisol to the inactive cortisone (Falcone & Little 1994), so that the fetus is not protected from the growth inhibiting actions of maternal cortisol (Lesage *et al.* 2001, Langley-Evans *et al.* 1996). The result is that a fetus of a poorly nourished woman could be exposed to higher concentrations of maternal cortisol, further reducing fetal growth.

Earlier program participation may have protected birth size through social pathways. Prenatal food programs, such as the MINIMat program or The Supplemental Nutrition Program for Women, Infants and Children (WIC) program in the US, provide opportunities for social contact. The early-invitation group likely had more social contact with the local food-supplement providers and with pregnant neighbors since they began the program earlier in pregnancy and consumed more food packets at the nutrition center. This increased social contact may have improved emotional well-being (Shaheen & Lindholm 2006, Collins *et al.* 1993, Oakley 1988) and social support, which are associated positively with birth weight (Feldman *et al.* 2000) regardless of self-reported stress (Dunkel-Schetter 2011, Nasreen *et al.* 2010, Collins *et al.* 1993, Oakley 1988). The manner in which these social factors influence birth outcomes is not clear, but one possible mechanism is that early-invitation may change health behaviors, such as resting more, that could improve birth outcomes (Orolanda *et al*. 2003).

Invitation time to start a prenatal food supplementation program did not modify the relationship of stress and birth size in females. Factors that influence fetal growth may differ by sex. The mechanisms for normal sexual dimorphism in birth size (Lampl *et al.* 2010, Clifton 2010, Kraemer 2003, Miles *et al.* 2010), and sex-specific differences in response to adverse events (Lampl *et al.* 2010) are actively being investigated, but they remain largely unknown. These mechanisms may include differences in placental function and structure, hormones, and growth factors, and may be Y chromosome-linked (Lampl *et al.* 2010, Clifton 2010, Miles *et al.* 2010). In one study, prenatal food supplements promoted growth and increased birth weight in males to a greater extent than in females (Mora *et al.* 1979), but in another study it did not (Kardjati *et al.* 1988). Under adverse conditions, males and females alter placental function differently leading to different growth and survival patterns.

Clifton (2010) provides evidence to support a hypothesis that males respond to one adverse event, such as maternal asthma (Murphy *et al.* 2003), by eliciting placental responses that maintain fetal growth, but increase the risk of intrauterine growth restriction if there is another adverse event. Females change placental genes and proteins to adapt to several insults, and reduce growth by a smaller amount than males. The results from our study are consistent with the pattern proposed by Clifton (2010), yet more research is needed to understand the biological mechanisms underlying sex-specific responses to growth promoting and growth inhibiting events.

Strengths and limitations

This study was a randomized controlled field trial conducted in community setting using a national nutrition intervention program as a type of control group. Additionally, a biomarker was used to measure stress, eliminating the potential for misinformation about sensitive topics that can occur with self-reported stress measures. Given that every pregnant woman received a food supplementation intervention, and social and health conditions may affect participation and response to interventions, generalizing to other contexts must be done cautiously. This study was conducted where the community has a long-standing relationship with ICDDR, B. Also, there was a potential to respond to a food intervention in this population as women of childbearing age suffer from chronic energy deficiency, pregnant women consume diets below recommended energy levels (Alam *et al.* 2003), and the prevalence of LBW is high (Khatun & Rahman 2008). Pregnant women could have partially or fully substituted the food packets for food at home, although the nutritional quality of food supplement may have been better than the food at home.

Conclusion

During pregnancy, poor maternal nutrition (Winkvist *et al.* 1998, Kardjati *et al.* 1988, Kramer 1987, Lechtig *et al.* 1975) and high stress (Dunkel-Schetter 2011, Field *et al.* 2008, Nasreen *et al.* 2010) can limit fetal growth and potentially limit human capital (Victora *et al.* 2008). This study demonstrates that a prenatal food supplement program, if delivered in the first trimester and of sufficient nutrient value, can ameliorate the negative influence of high maternal prenatal stress on birth weight of male infants. In low-income populations where women routinely face stressful life situations, and these situations are difficult to change, implementing prenatal food programs in the first trimester, earlier than is normally practiced, is one strategy that potentially can support better birth outcomes.

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Key Messages

Maternal stress in pregnancy limits fetal growth in a population where the prevalence of low birth weight is a public health concern.

Maternal nutrition and prenatal stress both influence birth size.

Early food supplementation can promote increased birth size of male infants whose mothers experienced higher prenatal stress.

Policy makers and program designers should consider providing food supplements in the first trimester of pregnancy to improve birth size in populations where maternal malnutrition and stress are high and low birth weight is of public health concern.

Table 1

Demographic, anthropometric (8 wk of gestation) and cortisol characteristics of Bangladeshi pregnant women by concentration of cortisol, invitation time to start food supplementation, or sex of infant in the Maternal Infant Nutritional Interventions Matlab study.

	Cortisol[a]		Food supplementation[b]		Sex		
	Lower *n*=527	**Higher *n*=514**	**Usual *n*=508**	**Early *n*=533**	**Male *n*=507**	**Female *n*=534**	**Total *N*=1041**
Body mass index	20.6 ± 2.7 [c,d]	19.8 ± 2.5	20.1 ± 2.6	20.3 ± 2.8	20.2 ± 2.6	20.2 ± 2.8	20.2 ± 2.7
Parity	1.5 ± 1.3[d]	1.3 ± 1.3	1.4 ± 1.4	1.4 ± 1.3	1.4 ± 1.4	1.4 ± 1.2	1.4 ± 1.3
Age (yrs)	27.1 ± 5.7 [d]	26.1 ± 5.7	26.5 ± 5.8	26.7 ± 5.6	26.7 ± 6.0	26.7 ± 6.1	26.6 ± 5.7
Wealth Index [e]	3.1 ± 1.4	3.0 ± 1.4	3.1 ± 1.4	3.0 ± 1.4	3.1 ± 1.4[d]	2.9 ± 1.4	3.0 ± 1.4
Cortisol (nmol/l)	7.3 ± 3.2[a]	12.8 ± 3.8	9.9 ± 3.2	9.8 ± 3.8	9.9 ± 3.4	9.7 ± 3.5	9.8 ± 3.5

[a] Cortisol obtained at 28-32 wk gestation was categorized as lower (≤ median value 9.6 nmol/l of cortisol) to indicate lower prenatal stress or higher (> median value 9.6 nmol/l of cortisol) to indicate higher prenatal stress.

[b] Invitation time to start food supplementation program was either early (~9 wk gestation) or usual (~20 wk gestation).

[c] Means ±SD (all such values).

[d] $p < 0.05$ t test between groups.

[e] Wealth Index 1 to 5 with 1 being the poorest and 5 being the wealthiest.

Table 2

Infant anthropometric and birth characteristics by concentration of prenatal maternal cortisol, invitation time to start food supplementation, in Bangladeshi pregnant women or infant sex in the Maternal Infant Nutritional Interventions Matlab study.

	Cortisol[a]		**Food supplementation**[b]		**Sex**	
	Lower *n*=527	**Higher *n*=514**	**Usual *n*=508**	**Early *n*=533**	**Male *n*=507**	**Female *n*=534**
Female (%)	52.4	50.2	49.6	52.9	---	---
Birth weight (g)	2744.9 ± 394.6 [c,d]	2677.9 ± 418.4	2697.2 ± 429.6	2728.6 ± 385.2	2745.8 ± 411.0[d]	2682.5 ± 402.2
Birth length (cm)	47.7 ± 2.1	47.5 ± 2.3	47.5 ± 2.2	47.7 ± 2.0	47.9 ± 2.2[d]	47.3 ± 2.2
Head circumference (cm)	32.6 ± 1.5 [d]	32.3 ± 1.8	32.5 ± 1.7	32.4 ± 1.6	32.7 ± 1.7[d]	32.2 ± 1.6
LBW (%)[e]	26.0	30.0	28.7	27.2	25.2[f]	30.5
Gestational age at birth (wk)	39.3 ± 1.5 [d]	38.9 ± 1.78	39.1 ± 1.7	39.1 ± 1.6	39.0 ± 1.6	39.2 ± 1.6

[a] Cortisol obtained at 28-32 wk gestation was categorized as lower (≤ median cortisol value 9.6 nmol/l) to indicate lower stress or higher (> median cortisol value 9.6 nmol/l).

[b] Invitation time to start food supplementation program was either early (~9 wk gestation) or usual (~20 wk gestation).

[c] Means ± SD (all such values).

[d] $p \leq 0.01$ *t* test between groups.

[e] Low birth weight (LBW) is < 2500 g adjusted birth weight. Measurements taken from 24 hr to 30 d after birth were adjusted using a standard deviation score transformation with the assumption that infants tend to remain relatively positioned in the anthropometric distribution during this time period.

[f] $p=0.03$ χ^2 test between groups.

Table 3

Interaction of maternal prenatal cortisol and invitation time to start the prenatal food supplementation program with birth weight (g), length (cm), and head circumference (cm) among Bangladeshi mothers and male infants in the Maternal Infant Nutritional Interventions Matlab study.

Males (*n*=507)	**Birth weight (g)**[a]		**Birth length (cm)**[a]		**Head circumference (cm)**[a]	
	β	***p***	**β**	***p***	**β**	***p***
Intercept	2945.3	<0.01	49.0	0.01	33.6	<0.01
Cortisol[b]	−20.1	0.01	−0.1	0.03	−0.1	0.01
Food supplement[c]						
Early	−259.4	0.02	−1.1	0.08	−1.1	0.02
Usual	0	0	0	0	0	0
Cortisol*Food Supplement						
Cortisol * Early	25.3	0.02	0.1	0.04	0.1	0.02
Cortisol * Usual	0	0	0	0	0	0
R2	0.014		0.020		0.018	

[a] Model controlling for type of micronutrient intervention (p > 0.05): Iron (60 mg) + 400 g folic acid (reference); Iron (30 mg) + 400 g folic acid; and Multiple micronutrients (MMN) that included 15 recommended micronutrients, including iron 30 mg, as described by Persson et al. (2012).

[b] Cortisol obtained at 28-32 wk gestation and was continuous.

[c] Invitation time to start food supplementation program was either early (~9 wk gestation) or usual (~20 wk gestation). Because of the inclusion of the interaction terms in the model, the coefficients for early-invitation food supplementation represent differences in anthropometry between early-invitation and usual-invitation when cortisol is zero.

Table 4

Interaction of maternal prenatal cortisol and invitation time to start the prenatal food supplementation program with birth weight (g), length (cm), and head circumference (cm) among Bangladeshi mothers and female infants in the Maternal Infant Nutritional Interventions Matlab study.

Females (*n*=534)	**Birth weight (g)[a]**		**Birth length (cm)[a]**		**Head circumference (cm)[a]**	
	β	***p***	**β**	***p***	**β**	***p***
Intercept	2719.1	<0.01	47.6	<0.01	32.6	<0.01
Cortisol[b]	−6.6	0.39	−0.1	0.68	−0.1	0.24
Food supplement[c]						
Early	5.2	0.96	0.4	0.52	0.6	0.90
Usual	0	0	0	0	0	0
Cortisol * Food Supplement						
Cortisol * Early	6.8	0.50	−0.1	0.76	−0.1	0.96
Cortisol * Usual	0	0	0	0	0	0
R2	0.011		0.005		0.007	

[a] Model controlling for type of micronutrient intervention ($p > 0.05$): Iron (60 mg) + 400 g folic acid (reference); Iron (30 mg) + 400 g folic acid; and Multiple micronutrients (MMN) that included 15 recommended micronutrients, including iron 30 mg, as described by Persson et al. (2012).

[b] Cortisol obtained at 28-32 wk gestation and was continuous.

[c] Invitation time to start food supplementation program was either early (~9 wk gestation) or usual (~20 wk gestation).