

Can Prevention of Low Birth Weight in Newborn may be Associated with Primordial Prevention of Cardiovascular Diseases and Type 2 Diabetes in Adult Life?

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Received: June 23, 2015

Revised: July 19, 2015

Accepted: July 23, 2015

Published online: October 10, 2015

ABSTRACT

Poor nutrition during pregnancy may be a risk factor for low birth weight and for irreversible health issues including obesity, type 2 diabetes, hypertension and hypercholesterolemia in adult life. Low birth weight has also been related to greater mortality from coronary artery disease (CAD) and type 2 diabetes in adult life. One earlier study from Northern Europe proposed that poor social conditions in childhood may be risk factor for obesity, diabetes and cardiovascular diseases (CVDs) in later life. It is possible that multiple confounders related to energy and micronutrient deficiencies may be interacting in the process of adaptations in critical time periods, during fetal, postnatal and child development. A review of literature on the effects on birth size and length of babies and of multiple micronutrient supplementation during pregnancy in low-income countries indicates that incidence of low birth weight may be decreased by

supplementation of about 15 micronutrients. This finding poses the possibility that for prevention of low birth weight, maternal micronutrient supplementation (15-20 nutrients) may be an important strategy. It is proposed that this strategy may lead the prevention of CVDs and type 2 diabetes in adult life. Cohort studies and long term follow up population based trials are needed to confirm this hypothesis.

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Key words: Hypertension; Nutrition; Diabetes; Inutro-undernutrition; Infant heart disease

Singh RB, Saboo B, Maheshwari A, Singh P, Verma NS, Singhal S, Sharma ZP. Can Prevention of Low Birth Weight in Newborn may be Associated with Primordial Prevention of Cardiovascular Diseases and Type 2 Diabetes in Adult Life?. *Journal of Cardiology and Therapy* 2015; 2(5): 425-429 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/1398>

INTRODUCTION

Human adaptations are a key to survival, which may extend life despite emergence of risk factors and diseases^[1-4]. The current increased susceptibility of people of Southwest Asia to coronary artery disease (CAD) and type 2 diabetes may be due to high prevalence of past undernutrition among pregnant women, resulting to low birth weight of South West Asians, that may have occurred about 30-50 years ago^[4]. Mothers eating an unhealthy diet characterized with low energy and micronutrients or Western diet during pregnancy, may be putting their children at risk of developing long term, irreversible health issues including obesity, greater levels of cholesterol and blood sugar as well as CVDs in adult life^[4-6]. The Tromsø heart study proposed that poor social conditions in childhood may be a

risk factor for obesity, diabetes and cardiovascular diseases (CVDs) in later life^[6]. In cross sectional surveys, micronutrient deficiency has been inversely associated with risk of CAD in India, which may be also common among pregnant women and fetus^[7-9]. The nutrient deficiency in mothers may result into increased risk of undernutrition including low birth weight, predisposing to CVDs and type 2 diabetes in later life^[7-9]. However, it is important to note that obesity in childhood can also be a risk factors for CAD in adult hood^[10]. It seems that Mediterranean style foods; micronutrient-rich vegetables, fruits or poultry, which are known to protect and metabolize can prevent oxidation of tissues and may protect against CVDs and type 2 diabetes in later life^[4].

BARKER'S HYPOTHESIS

Approximately 25 years ago, David Barker proposed that fetus and infant size were determinants of adult health. 'Barker's hypothesis' was based on the correlation of measurements of the weights and length of babies at birth as an index of fetal health and intrauterine growth^[5]. He also considered growth in infancy at 1 year and morbidity; CVDs, hypertension, stroke, diabetes and hyperlipidemia and mortality in later life. It was also pointed out by Singh *et al* in 1996 in a seminar discussion with David Barker that, apart from energy deficiency, micronutrient deficiency in pregnant women and fetus could be the underlying cause of increased risk of CVDs and type 2 diabetes in later life (personal communication)^[7]. There is evidence that both low birth weight and obesity in childhood are related to increased risk of coronary artery disease (CAD) in adults and recently have been associated with vascular endothelial dysfunction in children as well as in young adults^[5,8-13]. This is most marked in individuals with lower risk factor profiles and may be relevant to the pathogenesis of atherosclerosis in later life. Low birth weight has been related to mortality from CAD and to the development of obesity, hypertension and diabetes^[5,7,9]. These associations may be due to a direct effect of prenatal growth and conservative mechanisms developed due to physiological adaptations on the pathogenesis of early atherosclerosis, resulting into risk factors or due to alteration in the endothelial function and established atherosclerotic lesions^[1].

LOW BIRTH WEIGHT AND ENDOTHELIAL DYSFUNCTION

It is known that vascular endothelial dysfunction, associated with early growth may be a predisposing factor for atherosclerosis and in the development of CVDs^[11-13]. The influences of diet and lifestyle factors before and during pregnancy, on development of postnatal risk factors and their interaction on cardiovascular function and beta cells of pancreas or epigenetics remains poorly understood. However, multiple mechanisms have been proposed which may be related to a role of brain-related adaptations in metabolism of energy and nutrients via suprachiasmatic nucleus circadian clock, arcuate nucleus and preopiomelanocortin neurones.

The mechanism could be that the vascular wall function which is relevant to atherogenesis may be disturbed due to poor prenatal nutrition from early in life. These prenatal influences may cause epigenetic damage resulting in to hypomethylation of DNA and chromatids which amplify and increase the susceptibility for development of minor and major risk factors in adults. For example low birth weight enhances the susceptibility of the host in adult life, to have interaction with salt intake (blood pressures), obesity

(metabolic syndrome and diabetes), raised cholesterol (CAD) and smoking resulting in to related CVDs on modest increase in these factors. The increase in susceptibility is so high, that birth weight causes adverse effects on endothelium-dependent flow-mediated dilation (FMD) in children in the first decade of life before the acquisition of a significant risk factor burden^[11-13].

The 'Small Baby Syndrome' is characterized with low birth weight, which is a risk factor of diabetes, hypertension and CAD in adult life^[11]. Endothelial dysfunction is an important feature of these chronic diseases of adults. In one study among 19-20 year old subjects, randomly selected from low (<2.5 kg) and normal (3.0-3.8 kg) birth weight subjects, flow-related dilatation was impaired in low birth weight compared to normal birth weight subjects. It is concluded that endothelial dysfunction may be associated with fetal malnutrition, which may contributes to the clinical features of the diseases in later adult life. In a further study, 92 very low birth weight babies were compared with 68 born at term babies for FMD at age 18 to 27 years^[12]. Each 100-g of higher weight gain during the first 2 postnatal weeks was associated with 1.1% units higher FMD in adulthood among subjects with lowest birth weight. This study revealed that weight gain during the first postnatal weeks had no harmful effect on the arteries in young adulthood^[12]. In a further study in Finland, carotid intima-media thickness, brachial flow-mediated dilatation and cardiovascular risk factors were compared between young adults (24-45 years) born at term with impaired fetal growth (birth weight <10th percentile; *n*=207), born preterm (<37 weeks' gestation; *n*=253), and a control group born at term with normal fetal growth (birth weight 50-90th percentile; *n*=835)^[13]. It is interesting that subjects with impaired fetal growth had significantly greater triglycerides, C-reactive protein, low-density lipoprotein cholesterol, systolic blood pressure, and intima-media thickness as well as impaired FMD compared to normal growth subjects^[13]. It was concluded that impaired fetal growth, particularly preterm birth, may be associated with impaired endothelial function and elevated preclinical atherosclerosis in young adults, partly mediated by inflammation, blood pressure, and triglycerides^[13].

PRETERM BIRTH AND METABOLIC SYNDROME

Metabolic syndrome is a manifestation of insulin resistance which is greater among babies with low birth weight. A more recent meta-analysis of studies revealed that after 18 years of follow up, preterm birth, with gestational ages (born at <37-week) compared with birth at term (37- to 42-week) may be associated with manifestations of the metabolic syndrome^[14]. This analysis included 27 studies comprising of 17,030 preterm and 2,95,261 term-born adults. Preterm birth among adults was associated with significantly higher systolic blood pressure (mean difference, 4.2 mm Hg; *p*<0.001), diastolic blood pressure (mean difference, 2.6 mm Hg; *p*<0.001) as well as 24-hour ambulatory systolic blood pressure (mean difference, 3.1 mm Hg; *p*=0.03). The difference in low-density lipoprotein was also significant (mean 0.14 mmol/L; 95% CI, 0.05 to 0.21; *p*=0.01). In case of females, the preterm-term difference was more than the preterm-term difference in males by both systolic and diastolic blood pressures. It is clear that preterm birth was associated with higher blood pressure in adult life, with females having a higher risk than males. Increased plasma low-density lipoprotein in young adults born preterm may indicate a risk factor for atherosclerosis and CADs in later life^[14]. In the majority of outcome measures associated with the metabolic syndrome, this analysis indicated no difference between preterm and term born adults.

LOW BIRTH WEIGHT AND MICRONUTRIENT DEFICIENCY

Infants with birth weight <2.5 kg may differ from those < 10th percentile. In addition, neonates born in full-term may also be different from those born in pre-term. While neonates born in pre-term are indeed more likely to be with lower birth weight and the risk factors for them may somehow be different. It is possible that multiple confounders related to micronutrient deficiencies may be interacting in the process of adaptations in critical time periods during fetal and postnatal development^[1-3]. A mother or newborn may be more sensitive to environmental factors, which may worsen due to poor nutritional status of the fetus and mother resulting into low birth weight^[15-21]. There is evidence that micronutrient deficiency is widespread in the developing countries, more so, among pregnant women living in urban slums^[17-21]. Christan and Stewart reported that maternal micronutrient deficiency could be important in the fetal development as well as in the risk of chronic diseases^[22]. Singh et al and other workers also showed high prevalence of micronutrient deficiency to be important in the pathogenesis of adult diseases^[15-21]. Now several studies of multiple micronutrient supplementation during pregnancy on birth size and length of babies in low-income countries indicate that incidence of low birth weight may be decreased by supplementation of about 15-20 micronutrients^[23,25,26]. However, one meta-analysis of trials provided consistent evidence that supplementation providing approximately 1 RDA of multiple micronutrients during pregnancy did not result in any reduction in stillbirths or in early or late neonatal deaths compared with iron-folic acid alone^[24].

Recommendations by UNICEF/WHO/UNU for trial purposes include those 15 nutrients^[27]: 30 mg iron, 400 µg folic acid, 800 µg RE vitamin A, 200 IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 15 mg zinc, 2 mg copper, 65 µg selenium and 150 µg iodine. However, these recommendations may need further modification. It seems that adding chromium, magnesium, amino acids, omega-3 fatty acids and flavonoids could have additional benefits. Omega-3 fatty acids can enhance brain development among infants and prevent eclampsia, stroke, postprandial psychosis and depression in women^[16]. The supplementation of omega-3 fatty acid or fish and other foods rich in these fatty acids in pregnant women appears to be most important because it can directly modulate pathogenesis of brain related mechanisms^[28]. Experimental studies have demonstrated that deprivation of omega-3 fatty acids during pregnancy is associated with visual and behavioral deficits that cannot be reversed with postnatal supplementation^[28]. Fetal brain growth accelerates during the second half of pregnancy and the rate of growth remains high during the first year of life with continued growth for the next several years. It is likely that, during pregnancy, omega-3 requirements increase over normal to support fetal growth, particularly of the brain and eyes. Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to have multiple beneficial effects, including improving childhood development when ingested during pregnancy. Consensus guidelines have recommended that pregnant women consume at least 200 mg of DHA per day. It can be achieved by consuming 1 to 2 servings of seafood per week, dietary intake that is consistent with the current US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) advisory

In a landmark recent study, effects of antenatal multiple

micronutrient vs iron-folic acid supplementation on 6-month infant mortality and adverse birth outcomes were examined^[26]. In this study, women were provided supplements containing 15 micronutrients or iron-folic acid alone, taken daily from early pregnancy to 12 weeks postpartum, during a follow-up of 180 days. The findings revealed that among the 22,405 pregnancies in the multiple-micronutrient group and the 22,162 pregnancies in the iron-folic acid group, there were 14,374 and 14,142 live-born infants, respectively. There were 764 deaths (54.0 per 1000 live births) in the iron-folic acid group and 741 deaths (51.6 per 1000 live births) in the multiple-micronutrient group. Multiple-micronutrient supplementation resulted in a significant reductions in preterm births (18.6 vs 21.8 per 100 live births; RR, 0.85; 95% CI, 0.80-0.91; $p < 0.001$) and low birth weight (40.2 vs 45.7 per 100 live births; RR, 0.88; 95% CI, 0.85-0.91; $p < 0.001$). Thus, antenatal multiple micronutrients did not reduce all-cause infant mortality up to age 6 months. However, this therapy resulted in a significant reduction in low birth weight which indicate that these babies would be less susceptible to develop CVDs and type 2 diabetes in later adult life. This remarkable large trial confirms that nutrient administration in pregnant women appears to be a novel method for possible prevention of CVDs and type 2 diabetes in adults. There is no hard evidence to support that these babies would be less susceptible to develop CVDs and type 2 diabetes in later adult life. Longer follow up of these subjects for 30-40 years would confirm this conclusion.

POSSIBLE MECHANISMS

It seems that most of the investigators agree that Barkers Hypothesis of developmental programming, also referred to as “fetal origins of adult disease” is the basis for the observations on birth weight and risk of diseases^[5,6]. However, more specifically, it may be based on nutritional maladaptations by which low birth weight is not only associated with immediate morbidities for the neonate but also leads to later risk for adult diseases^[1]. It is possible that alteration to an individual’s metabolism related to conservation during the early periods of “plasticity” can remain permanent. The adaptations that occur during critical periods of fetal and postnatal development promote survival in an inadequate environment (ie, poor nutrition or growth restriction) due to a thrifty genotype^[1-5]. However, these subjects, later-in-life, on exposure to nutritional abundance and growth can cause metabolic disturbances that promote the development of diseases such as hypertension, obesity, and diabetes^[5,15,16,22]. Other hypothesis for the associations between in utero exposures and adult disease is that there are shared genetic risk factors and interactions with epigenetic markers such as methylation of DNA, that impact both early and later-life outcomes^[29,30]. It is also supported by the “fetal insulin hypothesis”, which posits that the same genetic factors that predispose to decreased fetal insulin secretion in utero may also affect insulin resistance in adulthood^[31]. It is possible that the intrauterine milieu, possibly due to adaptations, influences the development of the fetus as well as also the reproductive fitness of that fetus such that subsequent generations may continue to be affected or protected^[1,32,33].

In experiments, female rodents fed a low protein diet gave birth to offspring with low birth weight, reduced insulin sensitivity, and high cholesterol, whereas increased adiposity was more enhanced in female than male offspring^[34]. The gene expression analyses showed raised insulin-like growth factor-1 (IGF-1), insulin receptor substrate (IRS)-1, vascular endothelial growth factor (VEGF)-A, peroxisome proliferator-activated receptor-γ (PPARγ), leptin, adiponectin,

adipsin, lipoprotein lipase (LPL), Glut 1, Glut 3, but not Glut 4, mRNA expression in females fed the junk food diet throughout the study compared with females never given access to junk food. These females also give birth to offspring with metabolic conditions, despite being fed a normal diet which acts as unhealthy diet for them. It seems that metabolic conditions in the generation indicates that even in the absence of the original environmental stressor (poor nutrition), these offspring remain susceptible to metabolic conditions through transgenerational epigenetic inheritance^[32-35]. It seems that this is an important mechanism for the transmission of chronic diseases between generations that are inherited to the subsequent generations. It is known that about 30-40 years ago, the prevalence of underweight among new born babies was approximately 50%, which means that half of the adult population in the developing world today, should be at risk of developing CVDs and type 2 diabetes, and need more strict guidelines for prevention.

In brief, micronutrient supplementation during pregnancy can prevent low birth weight which possibly can decrease the risk of CVDs and type 2 diabetes in adult life. Long term controlled trials and cohort studies are necessary to confirm this consideration.

Conflict of interest has not been declared by the authors.

ACKNOWLEDGMENTS

International College of Cardiology for providing logistic support to help us writing this article.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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