論　文　概　要 (Thesis Abstract)

○論文題目　バングラデシュにおける胎児成長と臓器発達

(Theme)　Fetal growth and organ development in Bangladesh

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Summary

Introduction: Poor maternal nutritional status remains an important determinant of fetal growth, subsequent infant and child health, and survival. There is a wealth of experimental and epidemiological evidence linking early nutrition to later health outcomes, but there are very few intervention studies where these hypotheses may be tested. A limited number of studies determine the organ size relates to its function among children with the consequences of maternal and postnatal conditions. Research particularly in this area, is challenging and important for countries, like Bangladesh, where restricted fetal growth and infectious disease-related morbidity and mortality are still high and where there is a rapid emergence of chronic diseases such as hypertension, type II diabetes and kidney disease.

Objectives: The main purposes of the study were to examine the relationship between the early life growth impact on organ size and those functions in later life in the offspring of the MINIMat (Maternal and Infant Nutrition Intervention in Matlab) cohort at four and at nine years of age.

Specific objectives:

1) to determine childhood kidney size, and function in relation to early-life conditions at birth, with an especial focus on low birth weight (LBW).
2) to assess the effect of postnatal malnutrition trajectory on lung function at preadolescence.

Methods and materials: The present study was nested within the MINIMat cohort (trial registration: isrctn.org identifier: ISRCTN16581394) that is a large-scale study of combined interventions to improve maternal and infant health in Matlab, Bangladesh where a group of pregnant women was recruited over a 2-year period from November 2001 to October 2003. A total of 4436 women were enrolled to follow up with an ultrasound examination during clinic visits at 14, 19, and 30 weeks of pregnancy and fetal biometry measurements were conducted. In total, 3267 were singleton live births in the MINIMat trial. Infants in the MINIMat birth cohort were then followed up at 15 days and at 1, 2, 3, and 4 months. They were weighed, and their lengths measured every month until the age of 6 months and then every 2 months until the age of 1 year, and other follow-ups were conducted at the ages of 2 years, 4.5 years, and 9 years.

A cross-sectional assessment of the children's kidney size was conducted at 4.5 years of age and their glomerular filtration rate (eGFR) was estimated at the age of 9 years. Kidney volume was assessed on the sub-sample of 1067 full-term singleton child and these children were involved in the analysis of childhood kidney size in relation to birth weight status. At the age of 9 years, cystatin C was measured in 457 children of the 1067 children who were born at clinics (the immune cohort) to estimate the eGFR rate.

Moreover, at 9 years of age to assess lung function, the MINIMat study aimed to follow up 640 children, born within the MINIMat study from June 2003 to June 2004 and thus invited to perform the spirometry test (forced vital capacity, FVC; forced expiratory

volume per second, FEV1.0; maximum mid-expiratory flow, MMF; and peak expiratory flow, PEF).

Main results:

The study was embedded in a population-based prospective cohort of 1067 full-term singleton live births followed from fetal life onward. A change in status from LBW to NBW (normal birth weight) children, with kidney volume increases of 2.92 cm^3/m^2, after adjusting for covariates. One-unit change in kidney volume (cm^3/m^2) improved the eGFR to 0.18 mL/min/1.73m^2. The present study observed that the eGFR in LBW children had 5.44 mL/min/1.73m^2 less at the age of 9 years.

The present study observed that over half of the MINIMat cohort children have experienced a stunting phenomenon up to 9 years of age. Children who were persistently stunted showed a reduced mean FEV1.0/ml/s ($p<0.001$). Children with catch-up growth (height for age z-score) in all follow-ups especially at pre-school age showed a better lung function at the age of 9 years after adjusting for covariates.

Discussion:

The present study demonstrated the developmental origins of health and disease (DOHaD) hypothesis for the adult disease progression, and it has been observed that LBW children have a smaller size of kidney at the age of 4 years with a lessened eGFR at the age of 9 years. The progression of acute kidney injury and chronic kidney disease can be prevented

if the risk factors and disease states are diagnosed early. Worsening of kidney function can be slowed or averted by inexpensive interventions such as counseling for hypertension, tobacco control, promotion of physical activity and the reduction of salt intake.

We have also tested the association between longitudinal growth and lung function. We observed that children who catch-up growth showed a better lung function than the children who remain in the same growth as well as children who had faltering growth. The present study adds an evidence to adult disease development that the initiation of disease risk can be determined in early childhood. Thus, this study advocates the need for preventive measures for the LBW and the growth restricted children that must be given high priority in the future health care. In response to growing burden of non-communicable chronic disease, this study recommends improving monitoring of the risk group children, and the development of representative surveillance to reduce the prevalence of noncommunicable chronic diseases and associated risk factors and slower the disease progression.

Conclusions:

Low birth weight status leads to adverse effects on kidney size and function in children. Catch-up growth shows better lung function at preadolescence, suggesting that improving adequate height for age may modify postnatal lung function development. This study

provides a clear understanding of risk assessment of early-life predictors on chronic disease risk and indicates the initiation period of disease progression justifies the minimally invasive procedures are planned.