Undernutrition and Overnutrition During Pregnancy in India: Dual Teratogenesis

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India is one of the diabetes capitals of the world and at the same time the capital for low birth weight (LBW) and perinatal mortality. This paradoxical situation should have suggested a link between the two. This was recognized only recently after the pioneering studies by David Barker and his group in the United Kingdom, where they showed that LBW is a risk factor for future diabetes.[1] This is explained by the concept of fetal programming (ie, an irreversible effect on structure or function with long-term consequences). Fetal growth and development are influenced by an interaction between genetic factors and the intrauterine environment.

Fetal programming can manifest in various ways. It might affect size, body composition, and structure and function of systems, organs, and cells. Sometimes it may affect physiology without affecting size. It is increasingly appreciated that epigenetic changes are at the center of programming. These changes are mediated by methylation of DNA and acetylation of histones and through the role of microRNAs, all of which modify gene expression.

The Diabetes Unit at King Edward Memorial Hospital, Pune, India, has made important contributions to programming research. The original observation was that diabetes occurred in Indians at a much lower body mass index (BMI) compared to Europeans, which was possibly because of their higher central obesity and higher body fat percentage (adiposity). This led to the “thin-fat” Indian concept (Fig 1).[2,3] It also was noticed that Indians get diabetes at a much younger age.[4]

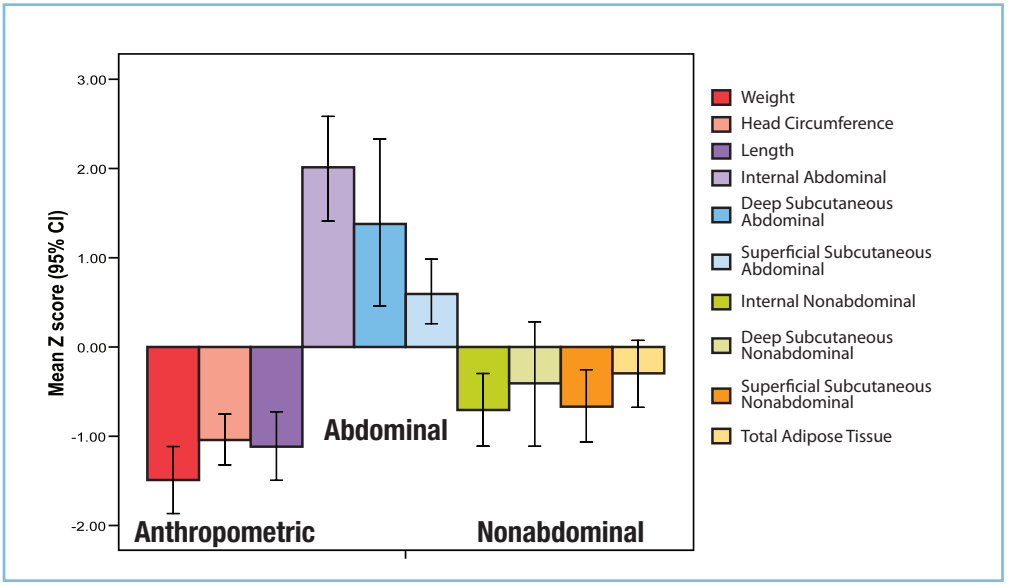

Fig 1. The 'thin-fat' Indian.[3] This figure shows the amount of body fat in Indian babies relative to that of English babies (standard deviation diagram). Indian babies are lighter, shorter, and thinner. They have a similar or smaller amount of nonabdominal fat, but higher amounts of both intra-abdominal and subcutaneous abdominal fat.

Fetal Growth and Programming

In 1991, researchers from King Edward Memorial Hospital joined Barker and Caroline Fall in the "fetal origins" research. The first collaborative research Pune Children Study confirmed that lower birth weight was associated with higher insulin resistance, as early as 4 years of age.[5] Children who were born small but grew big had the highest level of risk factors for diabetes and cardiovascular disease.[6] These findings suggested that intrauterine nutrition was possibly an important contributor to the risk of adult disease in Indians.

At the same time, it was known that fetal overnutrition, as in maternal diabetes, also increases the risk of obesity and diabetes in the child. A stage was set to investigate the factors influencing fetal growth and programming. This was the birth of the Pune Maternal Nutrition Study (PMNS), which was established in six villages near Pune in 1993. More than 800 pregnancies were studied. The children are visited every 6 months for anthropometric measurements, and parents and children are investigated every 6 years for a detailed assessment of body composition, cardiometabolic risk factors, and neurocognitive development.

The average mother in the PMNS was short (152 cm) and thin (BMI 18.1 kg/m^2), and gave birth to a light and thin baby (birth weight 2.7 kg, ponderal index 24.1). Interestingly, it was found that Indian babies were thin but fat (more adipose) compared to European babies, and that maternal intake of micronutrient-rich foods was a strong determinant of fetal size.[7] Paternal size predominantly influenced skeletal measurements, while baby's adiposity was predominantly determined by maternal factors. Short and fat mothers gave birth to the most adipose babies, suggesting an intergenerational influence of maternal early life "growth retardation" and her subsequent weight gain on body composition of the growing fetus.[8]

Follow-up of these children revealed that higher maternal folate in pregnancy predicted higher adiposity and insulin resistance at 6 years of age. The most insulin-resistant children were born to mothers who were vitamin B_{12} deficient and had high folate concentrations.[9] In addition, it was found that maternal vitamin B_{12} and folate predicted the child's neurocognitive function.[10] The Parthenon study in Mysore found that maternal vitamin B_{12} deficiency is associated with adiposity and gestational diabetes mellitus.[11] Thus, results in Indian studies point toward an important role for maternal one-carbon (1C) metabolism in fetal growth and programming. This is possibly because of the role of 1C metabolism in synthesis of nucleic acids, genomic stability, and the epigenetic regulation of gene function.

Noncommunicable Diseases

One of the challenges in the epidemiology of noncommunicable diseases (NCDs) in India is to reconcile the fact of rapid spread of the epidemic to the poor and the deprived, along with increasing affliction of the affluent. The finding of a disturbance in 1C metabolism in the undernourished (vitamin B_{12} and protein deficiency), as well as in the urban glucose-intolerant mothers (vitamin B_{12} deficiency associated with obesity and hyperglycemia), provides a unique explanation and an opportunity to tackle both fetal growth restriction (nutrient-mediated teratogenesis) and fetal macrosomia (fuel-mediated teratogenesis), which is referred to as a dual teratogenesis[12] (Fig 2).

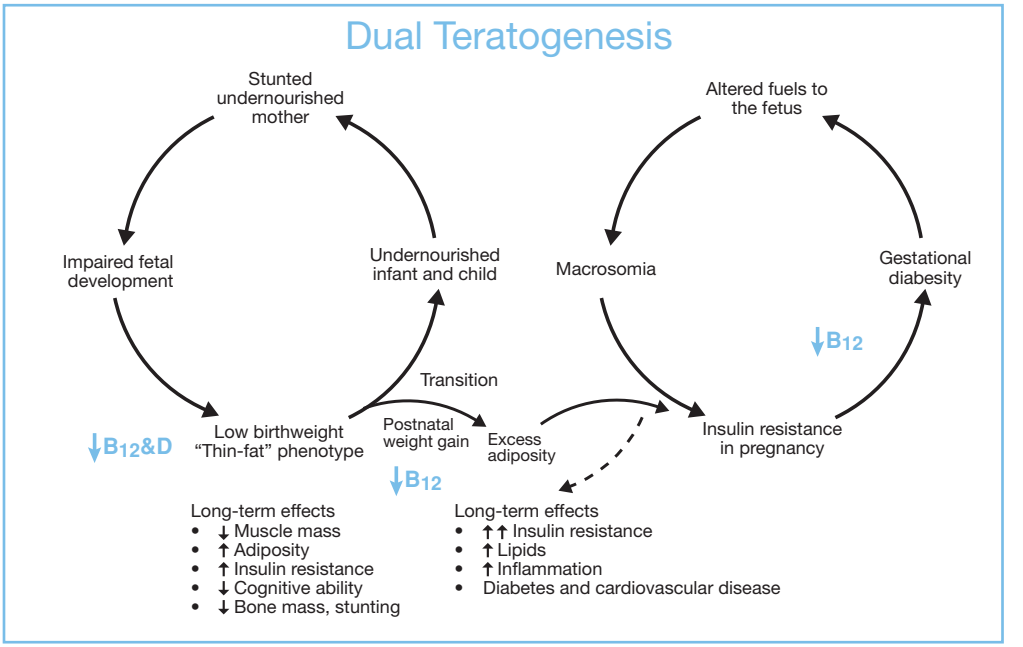

Fig 2. Dual teratogenesis.[12] This figure is a diagrammatic representation of the life cycles of babies born to undernourished and overnourished mothers (Indian and from other developing countries). Babies of undernourished mothers suffer intrauterine undernourishment and are born thin-fat. They are more insulin resistant. If postnatal nutrition levels are low, they remain thin-fat but "normal" adults and propagate the cycle. If these babies are overfed (on migration to cities or because of rapid economic transition), they become more adipose. Such mothers can develop gestational diabetes, which causes fetal macrosomia. Such babies are at higher risk of diabetes later in life. Research has shown an association of low circulating vitamin B_{12} with both the cycles, and vitamin D deficiency may play a role.

Thus, it is clear that a substantial proportion of adult health is programmed in utero. Health and nutrition of young girls is of paramount importance and is a major influence on the health of the next generation. The current idea of preventing NCDs in the middle-aged and elderly by difficult-to-do lifestyle adjustments is a very ineffective model. The next logical step in India is to improve 1C metabolism in adolescents for intergenerational prevention of adiposity, diabetes, and other related conditions. Improving the early life environment is perhaps more cost effective in preventing an NCD epidemic than controlling only the lifestyle factors in adults.

References

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Q & A

Q: Thank you for a fascinating presentation and amazing data. I am just puzzled about the observation that the effects of folate and B_{12} go in opposite directions, when my simple memory of the metabolic pathways is that there are synergistic effects in the homocysteine pathway.

I am just wondering whether you might see a contribution of folate and B_{12} that reflects certain dietary lifestyle patterns with people who are on a stricter vegan pattern with lower B_{12}, but with a high vegetable and folate intake. Is that a possible explanation? Are certain lifestyle factors and other dietary components or lifestyle components associated with this, perhaps causally, rather than folate and B_{12}?

Dr Yajnik: That is an excellent question. We have considered the possibility that our results are confounded by lifestyle factors, basically the protein intake, because protein and B_{12} go together. The Mendelian randomization results suggest that our nutritional associations are likely causal, but I am very willing to accept that there is still some confounded by lifestyle factors. This is the reason why in our planned intervention we have included a multi-micronutrients and milk arm to take care of other nutrients that might influence these associations.

Q: Indeed in the Mendelian randomization, I was not aware of the snips that you looked at for B_{12}. Is it also going in controversial directions then?

Dr Yajnik: They are going in the right direction. Holotranscobalamin levels represent the active form of B_{12}. As I showed, lower holotranscobalamin was associated with lower birth weight, indicating that B_{12} was contributing to fetal growth, and fucosyltransferase 2 *[FUT2]*, which is a marker for circulating B_{12}, again goes in the right direction on the prediction of insulin resistance in the child.

Just now, we are comfortable enough with what we have found to act on it. I am sure the story is more complex. There are a number of observations in the United States after folic acid fortification of flour—the imbalance between B_{12} and folate levels has widened. Normally in B_{12}-sufficient individuals, higher folate concentrations are associated with lower homocysteine concentrations. However, in vitamin B_{12}-deficient individuals, higher folate is associated with higher homocysteine and higher methylmalonic acid. Many papers in the United States have raised concerns about fortification of folic acid and the possible harmful effects it might have on a number of conditions, including anemia, neurocognitive decline, and some forms of cancer.