Indian J Med Res 137, February 2013, pp 249-250

Commentary

Maternal nutrition, nutrient transfer & foetal pancreas development

It is widely accepted that maternal intrauterine environment is associated with foetal growth, development and adult outcomes. In recent past, epidemiological studies have shown that an association exists between impaired intrauterine growth and susceptibility to adult chronic diseases such as type 2 diabetes[1]. The impaired intrauterine growth retardation/ restriction (IUGR) and low birth weight may occur due to a disagreement in maternal ability to provide nutrients and oxygen to foetus. The foetus responds in predictive and adaptive manner (PAR) to an inadequate amount of nutrients (glucose, amino acids and oxygen) in order to maximize its chances of survival[2]. It is reported in human studies that reduced supply of oxygen and critical nutrients results in a neonate with low ponderal index and assymetrical IUGR aptly mimicked in a few animal models[3]. The immediate response to undernutrition is catabolic consumption of substrates to provide energy[4]. It has been proposed that IUGR and various foetal growth patterns arise due to early stimulus/ insult that occurs during critical period of development affecting development and organization of critical organs/ tissues[5]. IUGR rat foetuses demonstrated metabolic profile characteristic of IUGR human foetuses such as hypoglycaemia, hypoxia, acidosis, and reduced concentration of insulin and insulin-like growth factor-I (IGF-I)[6]. It has also been revealed that low birth weight resulting due to maternal undernutrition is associated with insulin resistance, impaired glucose tolerafnce, hyperlipidaemia and type 2 diabetes[7]. Thus, the proposition that the placenta may act as nutrient sensor with the mammalian target of rapamycin kinase (mTOR) having a major part in nutrient sensing pathway[8], along with prolonged undernutrition may influence the foetus to change its metabolic rate, alter hormone production and tissue sensitivity to hormones, for example, decrease in foetal insulin and IGF-I[9,10]. During such conditions the blood flow is redistributed to protect key organs such as brain leading to impaired development of muscle, kidneys and endocrine pancreas[11]. The most extensively studied low-protein animal models of early growth restriction have been correlated to human populations with similar dietary intakes and subsequent outcomes. Studies have shown that animals with 50 per cent restriction of energy intake during last week of pregnancy led to microsomic pups, which had impaired beta cell development with reduced plasma glucose and insulin concentrations[12,13]. It is demonstrated that neonates of protein restricted dams have impaired pancreatic development such as pancreatic islet vascularization, reduced islet size, reduced beta cell mass, and reduced insulin content[14] due to reduced beta cell proliferation and increased apoptosis[13,15]. It is also demonstrated that the transcription factor 'pancreatic duodenal homeobox-1' (Pdx-1) expression is reduced, which regulates array of genes that contribute to the development of pancreas. Thus disruption of Pdx-1 may lead to absence of insulin producing cells and arresting early pancreatic development[16,17]. Additionally, IGF-II reduced expression was observed in foetal and neonatal islet cells of growth-restricted rats (bilateral uterine ligation model)[18] of uteroplacental insufficiency. Such model demonstrated glucose intolerance and insulin resistance at an early age (1 wk) and mild fasting hyperglycaemia and hyperinsulinaemia by 7-10 wk of age, followed by reduction in beta cell mass preceded by impairment in the first phase insulin secretion in response to glucose stimulation[19]. It was further reported that in this model the arginine stimulated insulin release was similar to control rats, and the loss of glucose stimulated insulin response is caused by intrinsic defect in the β-cell induced by uteroplacental insufficiency. Progressive impairment of glucose tolerance thus led to overt diabetes by 6 months of age as beta cells failed to compensate for secretory defects and insulin resistance[19]. Although the Dutch Famine Study has been insightful[20-22], studies relating maternal nutrition to the development of human pancreas and their potential impact in adult life are lacking. The study by Uday Kumar *et al* in this issue[23] links together data correlating maternal nutrient status and the development of pancreas obtained from mid-gestational age. One of the advantages of the study is that it undertakes the

analysis of second trimester human foetal pancreas for identifying morphometric changes to development of insulin producing cells. The limitation however, is the small number of samples assessed in this study and the lack of functional analyses to identify the role of maternal nutrient status on glucose-insulin metabolism. Studies carried out in animal models of intrauterine growth retardation and low-protein diet during gestation have confirmed that the second trimester is an important age for development of insulin producing cells and also for their biochemical maturation[14,18,24]. The limitation of most human studies has been accessibility to second trimester human pancreas for ethical and other reasons. However, Uday Kumar and colleagues[23] have been able to collect a small, yet significant, number of samples from second trimester human foetuses. Although the investigators do not find significant differences in the morphometry of foetal pancreas from different maternal nutrient groups, further studies related to understanding the function of insulin producing cells from such pancreatic islets need to be carried out. These studies would potentially help in understanding the differences, if any, between glucose-insulin metabolism and maternal nutrition in well characterized human pancreatic samples.

Sarang N. Satoor &
Anandwardhan A. Hardikar*
Diabetes & Islet Biology Group/
NHMRC Clinical Trials Centre
Level 6, Medical Foundation Building
92-94 Parramatta Road
Camperdown NSW 2050
Australia
**For correspondence*:
anand.hardikar@ctc.usyd.edu.au

References

1. Reusens B, Ozanne SE, Remacle C. Fetal determinants of type 2 diabetes. *Curr Drug Targets* 2007; *8* : 935-41.
2. Wells JC. The thrifty phenotype: An adaptation in growth or metabolism? *Am J Hum Biol* 2011; *23* : 65-75.
3. Wigglesworth JS. Fetal growth retardation. Animal model: uterine vessel ligation in the pregnant rat. *Am J Pathol* 1974; *77* : 347-50.
4. Harding JE, Johnston BM. Nutrition and fetal growth. *Reprod Fertil Dev* 1995; *7* : 539-47.
5. Barnes SK, Ozanne SE. Pathways linking the early environment to long-term health and lifespan. *Prog Biophys Mol Biol* 2011; *106* : 323-36.
6. Ogata ES, Bussey ME, Finley S. Altered gas exchange, limited glucose and branched chain amino acids, and hypoinsulinism retard fetal growth in the rat. *Metabolism* 1986; *35* : 970-7.
7. Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition* 1997; *13* : 807-13.
8. Jansson T, Powell TL. IFPA 2005 Award in Placentology Lecture. Human placental transport in altered fetal growth: does the placenta function as a nutrient sensor? - a review. *Placenta* 2006; *27* (Suppl A): S91-7.
9. Fowden AL. Endocrine regulation of fetal growth. *Reprod Fertil Dev* 1995; *7* : 351-63.
10. Fowden AL, Giussani DA, Forhead AJ. Endocrine and metabolic programming during intrauterine development. *Early Hum Dev* 2005; *81* : 723-34.
11. Rudolph AM. The fetal circulation and its response to stress. *J Dev Physiol* 1984; *6* : 11-9.
12. Garofano A, Czernichow P, Breant B. Beta-cell mass and proliferation following late fetal and early postnatal malnutrition in the rat. *Diabetologia* 1998; *41* : 1114-20.
13. Bertin E, Gangnerau MN, Bellon G, Bailbe D, Arbelot De Vacqueur A, Portha B. Development of beta-cell mass in fetuses of rats deprived of protein and/or energy in last trimester of pregnancy. *Am J Physiol Regul Integr Comp Physiol* 2002; *283* : R623-30.
14. Snoeck A, Remacle C, Reusens B, Hoet JJ. Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas. *Biol Neonate* 1990; *57* : 107-18.
15. Desai M, Crowther NJ, Lucas A, Hales CN. Organ-selective growth in the offspring of protein-restricted mothers. *Br J Nutr* 1996; *76* : 591-603.
16. Arantes VC, Teixeira VP, Reis MA, Latorraca MQ, Leite AR, Carneiro EM, *et al*. Expression of PDX-1 is reduced in pancreatic islets from pups of rat dams fed a low protein diet during gestation and lactation. *J Nutr* 2002; *132* : 3030-5.
17. Iype T, Francis J, Garmey JC, Schisler JC, Nesher R, Weir GC, *et al*. Mechanism of insulin gene regulation by the pancreatic transcription factor Pdx-1: application of pre-mRNA analysis and chromatin immunoprecipitation to assess formation of functional transcriptional complexes. *J Biol Chem* 2005; *280* : 16798-807.
18. Petrik J, Reusens B, Arany E, Remacle C, Coelho C, Hoet JJ, *et al*. A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II. *Endocrinology* 1999; *140* : 4861-73.
19. Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. *Diabetes* 2001; *50* : 2279-86.
20. Stein AD, Lumey LH. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. *Hum Biol* 2000; *72* : 641-54.
21. Stein AD, Ravelli AC, Lumey LH. Famine, third-trimester pregnancy weight gain, and intrauterine growth: the Dutch Famine Birth Cohort Study. *Hum Biol* 1995; *67* : 135-50.
22. Susser M, Stein Z. Timing in prenatal nutrition: a reprise of the Dutch Famine Study. *Nutr Rev* 1994; *52* : 84-94.
23. Uday Kumar P, Ramalaxmi BA, Venkiah K, Sesikeran B. Effect of maternal undernutrition on human foetal pancreas morphology in second trimester of pregnancy. *Indian J Med Res* 2013; *137* : 302-7.
24. Dahri S, Snoeck A, Reusens-Billen B, Remacle C, Hoet JJ. Islet function in offspring of mothers on low-protein diet during gestation. *Diabetes* 1991; *40* (Suppl 2): 115-20.