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Letters

Observations

Paternal insulin resistance and fetal growth: problem for the 'fetal insulin' and the 'fetal origins' hypotheses

To the Editor: Hattersley and Tooke proposed a genetic explanation, "the fetal insulin hypothesis" for the relationship between poor intrauterine growth and increased risk of diabetes and cardiovascular disease [1]. They suggest that this relationship could be due to a common genetic antecedent rather than intrauterine malnutrition ('fetal origins') [2]. The genetic mechanisms which regulate insulin secretion and/or insulin action can influence fetal growth because insulin is a growth factor during in utero life [3]. The hypothesis predicts that a child's birth weight and the more specific measures of insulin-mediated growth would show an inverse correlation with paternal insulin resistance. A study in Pima Indians demonstrated that the children born to diabetic fathers had low birth weight after the influence of maternal gestational diabetes was removed [4]. We tested the paternal prediction of the 'fetal insulin hypothesis' in data from the Pune Maternal Nutrition Study, a study of fetal growth in rural India [5].

We studied parental size, maternal nutrition and fetal growth in six villages near the city of Pune, India. A total of 2675 eligible women were visited every month to record their last menstrual date and every 3 months to make detailed anthropometric measurements. Pregnant women ($n = 814$) serially enrolled before 21 weeks' gestation were studied twice during pregnancy (18 and 28 weeks) for nutritional assessment (anthropometry, dietary intake, physical activity and circulating concentrations of nutrients). Maternal glucose tolerance was assessed by 75 g oral glucose tolerance test at 28 weeks' gestation. The fathers' anthropometry was recorded and a 75 g oral glucose tolerance test carried out. Plasma concentrations of specific insulin, proinsulin and 32–33 split proinsulin were measured as described [6]. Seven hundred and seventy babies were delivered and measured in detail at birth. Three mothers developed pregnancy-induced hypertension and were excluded from the analysis. This analysis is restricted to 633 full term, singleton babies and their parents.

The parents and the babies were small and thin compared with Western populations (Table 1). One mother was found to have diabetes and two had impaired glucose tolerance (IGT) (WHO 1985 criteria) at 28 weeks' gestation. Maternal BMI and height were significant predictors of child's birth weight ($r = 0.14$, $p < 0.001$, $r = 0.16$, $p < 0.001$ respectively). Maternal fasting plasma glucose concentration at 28 weeks' gestation was directly related to the birth weight of the baby ($r = 0.10$, $p < 0.05$, all correlations controlled for gestation at delivery, maternal parity and sex of the baby) and to the baby's mid-upper arm circumference ($r = 0.12$, $p < 0.01$) but not to skinfold thicknesses (triceps and subscapular), head circumference, height or placental weight. Maternal insulin resistance (HOMA-R, calculated from the Homeostasis Model [7]) was related to child's birth weight ($r = 0.08$, $p = 0.06$) (Fig. 1) but not to any other fetal parameters. This relationship was independent of maternal BMI. Maternal fasting plasma proinsulin concentration was not related to birth weight but split 32–33 proinsulin concentration was significantly related ($r = 0.10$, $p < 0.02$).

Of 497 fathers tested, one was found to have diabetes and 13 IGT. Paternal and maternal BMI were related ($r = 0.16$, $p < 0.001$). Paternal BMI and waist circumference were related to the baby's birth weight ($r = 0.13$, $p < 0.01$, $r = 0.11$, $p < 0.05$, respectively) and remained so when corrected for maternal BMI. Paternal height and waist-to-hip ratio were not related to baby's birth weight. Paternal 2 h plasma glucose concentration (but not fasting) was related to the birth weight of the baby ($r = 0.09$, $p < 0.05$, corrected for gestation at delivery, sex of the baby and maternal parity) and to placental weight ($r = 0.13$, $p < 0.01$). Paternal insulin resistance (HOMA-R) was directly related to birth weight ($r = 0.10$, $p < 0.05$) (Fig. 1), to mid-upper arm circumference ($r = 0.10$, $p < 0.05$) and placental weight ($r = 0.11$, $p < 0.05$) but not to baby's skinfold thicknesses (triceps and subscapular), head circumference or height. Relation of paternal glucose and insulin resistance with baby's size were not independent of paternal BMI. Paternal fasting plasma proinsulin and split 32–33 split proinsulin concentrations were not significantly related to fetal birth weight.

Thus, in our study, both maternal and paternal size, glycaemia and insulin resistance were directly related to baby's birth weight and to mid-upper arm circumference. Maternal influence on fetal growth can be genetic and/or through the intrauterine environment (metabolic, vascular etc). Paternal influence will operate through genetic mechanisms provided the effect of 'assortative mating' is ruled out. In our data the relationship between paternal and neonatal size remained significant after controlling for maternal size and would thus support a genetic influence on fetal growth. Primacy of paternal BMI rather than insulin resistance in determining fetal birth weight suggests that the paternal influence could operate through control of body size rather than metabolism. This could operate through placental size and function as suggested by a significant relationship between paternal size and insulin resistance and placental weight.

The 'fetal insulin hypothesis' explains the association between mutations affecting beta-cell function and poor intrauterine growth. It also highlights the importance of intrauterine environment (hyperglycaemia) on fetal growth. However,

Table 1. Characteristics of full-term babies, their mothers and fathers in the Pune Maternal Nutrition Study

	Babies (n = 633)	Mothers (n = 633)	Fathers (n = 599)
Age	39 (weeks) (1.2)	21 years (3.5)	28 years (4.6)
Weight (kg)	2.665 (0.3)	41.7 (5.1)	52.9 (8.0)
Height (cm)	47.8 (2.0)	152 (5.1)	165 (6.2)
Body mass index	24.5(g/cm^3) (0.2)	18.1(kg/m^2) (1.9)	19.5(kg/m^2) (2.5)
Plasma glucose (mmol/l)			
Fasting		4.0 (0.6)	5.0 (0.8)
2-h OGTT		4.4 (1.1)	5.1 (1.2)
Plasma insulin (pmol/l)			
Fasting		16.0 (10.0–24.0)	22.0 (13.0–35.0)
2-h OGTT		78.0 (34.3–135.0)	87.0 (46.0–149.0)
Plasma proinsulin (pmol/l)		2.5 (1.25–3.0)	3.2 (1.2–4.0)
Plasma 32–33 split proinsulin (pmol/l)		3.4 (1.25–3.8)	3.3 (1.2–4.0)
HOMA-R[a]		0.55 (0.37–0.81)	0.86 (0.54 – 1.33)

Figures represent means ± SD or median (interquartile range). Maternal age and anthropometry represent pre-pregnant measurements, plasma glucose and insulin concentrations (fasting and 2-h OGTT during a 75 g oral glucose tolerance test) and HOMA-R at 28 weeks' gestation.

[a] HOMA-R is the calculated insulin resistance by the HOMA[7] model

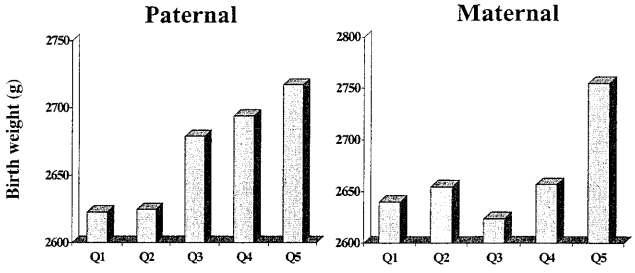

Fig. 1. Child's birth weight by quintiles of maternal (28 weeks' gestation) and paternal insulin resistance (HOMA model[6]). The significance is corrected for gestational age and sex of the child in case of fathers ($p < 0.05$) and additionally for parity in case of mothers ($p = 0.06$)

mutations affecting beta-cell function are rare. Insulin resistance, on the other hand, plays a major part in the pathogenesis of Type 2 (non-insulin-dependent) diabetes mellitus and precedes beta-cell deficiency by many years. Geneticists have ascribed insulin resistance to a 'thrifty gene' [8] but as yet no consistent marker has emerged. This means that at present the insulin resistance aspect of the 'fetal insulin hypothesis' cannot be tested by molecular genetic studies. Our results of the direct relationship between paternal insulin resistance (phenotype) and fetal growth are contrary to the predictions of the hypothesis. This was true for birth weight as well as mid-upper arm circumference which represents fetal 'muscle', one of the insulin-sensitive tissues. It is of note that the 'fetal origins' [2] and the 'thrifty phenotype' [9] hypotheses do not consider paternal influences on fetal growth and future risk of disease.

Our results suggest that both maternal and paternal size and metabolic factors predict fetal size. Insulin resistance could be an important mechanism influencing fetal growth. This observation could have important implications for future research in 'fetal origins' and the possible interventions to influence fetal growth.

C. S. Yajnik, K. J. Coyaji, C. V. Joglekar, S. Kellingray, C. Fall

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Corresponding author: Dr. Chittaranjan S. Yajnik
Diabetes Unit, King Edward Memorial Hospital
and Research Centre, Rasta Peth, Pune 411 011, India