# Prematurity and Insulin Sensitivity

V. Mericq

Institute of Maternal and Child Research, Faculty of Medicine, University of Chile, Santiago, Chile

**Key Words**

Glucose · Insulin · Intrauterine growth retardation · Preterm · Small for gestational age

**Abstract**

Premature infants of low and extremely low birth weight represent a challenge for neonatal intensive care units and paediatricians. These neonates may be at increased risk of insulin resistance and diabetes perinatally and during childhood. During the first week of postnatal life, infants born prematurely are at risk of abnormalities in glucose homeostasis. Additionally, there are major differences in their glucose/insulin homeostasis compared with infants born at term. Preterm infants are at risk of hypoglycaemia, due to decreases in deposits of glycogen and fat that occur during the third trimester, and also to transient hyperinsulinaemia. Hyperglycaemia may also be observed in preterm infants during the perinatal period. These infants are unable to suppress glucose production within a large range of glucose and insulin concentrations, insulin secretory response is inappropriate, insulin processing is immature and there is an increased ratio of the glucose transporters Glut-1/Glut-2 in fetal tissues, which limits sensitivity and hepatocyte reaction to increments in glucose/insulin concentration during hyperglycaemia. In addition, increased concentrations of tumour necrosis factor α present in intrauterine growth retardation (IUGR) and induce insulin resistance. It has been proposed that the reduced insulin sensitivity may result from adaptation to an adverse in utero environment during a critical period of development. We have investigated postnatal insulin resistance in 60 children born with very low birth weight and either small for gestational age or at an appropriate size for gestational age. This study showed that IUGR, rather than low birth weight itself, was associated with increased fasting insulin levels. As poor fetal growth may be associated with the development of obesity, type 2 diabetes and the metabolic syndrome in later life, it is important that we continue to increase our understanding of the effects of IUGR on postnatal growth and metabolism.

## Introduction

Advances in medicine, and specifically in neonatal care, have allowed an increased proportion of premature infants of low and extremely low birth weight to survive. These infants represent a challenge for neonatal intensive care units and paediatricians. However, as recent data indicate an association between birth weight and adult disease, considerable interest in the lives of these premature infants has been raised. As many of the advances in neonatal care have taken place over the last 3–4 decades, it may be too soon to examine the long-term consequences. In this paper, however, we will examine the available evidence for a link between prematurity and insulin sensitivity and glucose homeostasis in the perinatal period and during infancy and childhood.

V. Mericq
Institute of Maternal and Child Research
Faculty of Medicine, University of Chile
Casilla 226-3, Santiago (Chile)
Tel. +56 2 424 8280, Fax +56 2 424 7240, E-Mail vmericq@med.uchile.cl

## Insulin Sensitivity and Glucose Homeostasis during the Perinatal Period

During the first week of postnatal life, infants born prematurely are at risk of abnormalities in glucose homeostasis. Additionally, there are major differences in glucose/insulin homeostasis compared with infants born at term. For example, premature infants of very low birth weight always require parenteral glucose administration.

Several ethical restrictions limit research in the perinatal period in these infants. Studies should not be invasive; blood samples should be minimized and withdrawn from peripheral vessels but should allow obtained data to be extrapolated to other inaccessible tissues, and the smallest possible sample of patients should be examined. These limitations have been overcome by kinetic studies using isotopic substances together with the availability of mass spectrometric quantification.

*Glucose Production*

All available studies of glucose production in preterm neonates have used intravenous glucose injected at different rates. In preterm infants, glucose is continuously produced at similar rates to those in term newborns, even when glucose is administered intravenously. In fact, there is a negative correlation between glucose production and birth weight in preterm infants. Complete suppression of glucose production occurs only when the glucose concentration reaches 250 mg/dl. This contrasts with experience in adults, where glucose production is suppressed when this glucose is administrated parenterally at a rate similar to or greater than endogenous production. To evaluate whether this effect is related to insulin sensitivity, a hyperinsulinaemic-euglycaemic clamp has been performed in newborns [1]. When insulin was administered at rates of 0.5–4.0 mU/kg/min, there was a decrease of 41–58% in glucose production, compared with values before insulin administration. The result is similar in term and preterm newborns and is in remarkable contrast to the adult response during the clamp: in adults, a dose of 2 mU/kg/min of insulin achieves a maximum insulin effect on both glucose production and glucose utilization [2].

These differences are most likely related, at least in part, to the ontogeny of glucose transporters (Glut-2) in the liver and pancreatic beta cells. Glut-1 is the predominant glucose transporter isoform in fetal tissues and is characterized by a high glucose affinity and efficiency in transporting glucose through the organs. After birth, the concentration of Glut-1 decreases, while concentrations of Glut-2 in the liver, Glut-3 in the brain and neurones and Glut-4 in muscle increase. Glut-1 continues to have an important role in the blood-brain barrier, however, and Glut-3 regulates glucose uptake by neurones. Concentrations of Glut-1 are negatively regulated by glucose but have no effect on Glut-3. On the other hand, insulin positively regulates Glut-4 in muscle and adipose tissue. There is agreement that glucose utilization (oxidative and non-oxidative) is related to the rate of intravenous glucose administration and plasma glucose and insulin concentrations, but it is not clear when the plateau is reached for each of these factors. Importantly, during the perinatal period the ratio of oxidative/non-oxidative glucose utilization decreases. As a consequence of this deregulation in the glucose/insulin axis, frequent abnormalities occur in glucose homeostasis during the perinatal period in preterm infants.

*Hypoglycaemia*

Controversy exists regarding the definition of hypoglycaemia, and the reported incidence in preterm infants therefore varies from 7 to 57%. Recently, Battaglia et al. [3] reported cord glucose concentrations to be between 54 and 108 mg/dl, which appears to indicate that target blood glucose concentrations should be over 60 mg/dl during this period, similar to those in other periods of life. This recommendation is based on studies of preterm infants in which the number, frequency or intensity of hypoglycaemic episodes were negatively correlated with neurodevelopment. Preterm infants are at risk of hypoglycaemia, mainly due to a decrease in deposits of glycogen and fat that occurs during the third trimester, mostly after week 34 of gestation, as shown by cord leptin concentrations [4]. In addition, the ratio of brain size to body size is increased in preterm infants, and nearly 90% of glucose utilization is by the brain. As alternative substrates are not available in preterm newborns, the brain is left unprotected from hypoglycaemia. Levitsky et al. [5] showed that ketone bodies and non-esterified fatty acid concentrations are decreased in preterm newborns compared with those born at term. Glucose sensing is also immature in beta cells [6], which could contribute to the decreased insulin regulation during hypoglycaemia.

Hypoglycaemia can also occur in preterm infants as a consequence of transient hyperinsulinaemia or so-called stress-induced hyperinsulinaemia. In this case, persistent neonatal hypoglycaemia develops due to hyperinsulinaemia that subsequently resolves. Patients with this form of hyperinsulinaemia have normal sulphonylurea receptors and glutamate dehydrogenase function, so the aetiology

is different from the known genetic causes of hyperinsulinaemia. Transient hyperinsulinaemia has been reported to occur more frequently in infants suffering from perinatal asphyxia, in those with intrauterine growth retardation (IUGR) and in cases of maternal toxaemia. In a study reported by Hoe et al. [7], the mean duration of transient hyperinsulinaemia was 5.5 months, with a range of 2 weeks to 11 months. These patients usually require high loads of intravenous glucose and have a positive response to diazoxide and glucagon.

*Hyperglycaemia*

Hyperglycaemia is the other abnormality in glucose/insulin homeostasis that can be present during the perinatal period, with an incidence as high as 68% in preterm infants. This contrasts with 5% encountered in term newborns. As explained above, preterm infants are unable to suppress glucose production within a large range of glucose and insulin concentrations, the insulin secretory response is inappropriate, insulin processing is immature and there is an increased ratio of Glut-1/Glut-2 in fetal tissues, which limits sensitivity and hepatocyte reaction to increments in glucose/insulin concentrations during hyperglycaemia. In addition, increased concentrations of tumour necrosis factor α are present in the perinatal period after IUGR, which induce insulin resistance [1].

Currently, there is agreement that glucose concentrations in the newborn should be maintained between 60 and 150 mg/dl. This is particularly important, as glucose transporters might be programmed during critical windows of development, and exposing the newborn to high concentrations of glucose could have important postnatal consequences. All the conditions described above should encourage caution when assessing insulin sensitivity at this early time after birth in preterm newborns.

## Insulin Sensitivity in Preterm Infants Born Small for Gestational Age (SGA) versus Those Born at an Appropriate Size for Gestational Age (AGA)

There are only a few studies of glucose/insulin abnormalities within the perinatal period that compare infants who were born SGA with those born AGA.

To investigate whether IUGR is associated with decreased sensitivity to insulin and the effect of glucocorticoid therapy, Leipala et al. [8] used an abbreviated minimal model to study insulin sensitivity in preterm newborn infants at a mean of 7 ± 3 days with a birth weight of less than 1,500 g. Basal insulin sensitivity and insulin sensitivity index did not differ between infants born AGA and those born SGA, but steroids decreased insulin sensitivity only in the SGA group.

A similar observation was performed in a larger group of preterm newborns in South Africa [9]. One-hundred premature infants were recruited, and fasting and postprandial (standardized milk feed) glucose/insulin levels were measured. Assessment occurred within 1–65 days after birth. Infants born SGA had higher 60-min insulin levels than neonates born AGA, despite similar glucose levels. As we have recently described for a term cohort [10], this study also found that postnatal growth velocity correlated negatively and independently with birth weight and insulin resistance.

## Insulin Sensitivity during Childhood in Individuals Born Preterm and SGA versus Those Born Preterm and AGA

Interest in studying insulin sensitivity in preterm infants later in life increased after reports during the last decade linking low birth weight to cardiovascular disease, impaired glucose tolerance and type 2 diabetes mellitus. Initial observations were made in retrospective studies of British adults [11], but later these observations were replicated in young adults and children with different ethnic backgrounds. It has been proposed that reduced insulin sensitivity is the hallmark in most low birth weight-related conditions, and may result from adaptation to an adverse environment during a critical period of development in utero. In this model, birth weight is assumed to be a proxy for the prenatal environment. However, it is well known that newborns with low birth weight are also exposed to stressful conditions postnatally, which is reflected in higher neonatal morbidity and mortality. This has led to the hypothesis that postnatal morbidity may also contribute to the metabolic modifications observed in children of low birth weight, independently of their gestational age. Therefore, if early postnatal morbidity is relevant in conditioning long-term metabolic changes, prematurity may be an important confounding factor that was not assessed in historical cohort studies. In addition, it has been suggested that the metabolic consequences of low birth weight may be mediated by an accelerated rate of postnatal growth.

We have recently shown in a prospective cohort of infants born SGA at full term that fasting and post-load insulin levels are directly related to the extent of centile

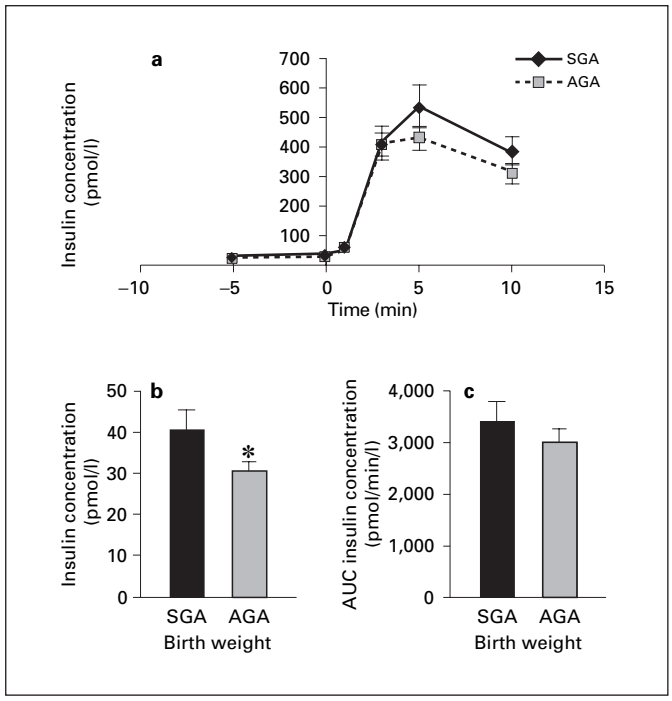


**Fig. 1.** Serum insulin levels during a short intravenous glucose tolerance test (sIVGTT) in children aged 5–7 years, of very low birth weight, who were small for gestational age (SGA; n = 20) and an appropriate size for gestational age (AGA; n = 40). **a** Insulin profile during the sIVGTT. **b** Fasting insulin levels (mean of values taken at −5 and 0 minutes). **c** Postload insulin secretion, evaluated as the area under the curve (AUC) for insulin. Data are expressed as mean ± SEM. * $p < 0.05$. Adapted from [12] with permission.

crossing in weight and height during the first year of life [12]. To investigate determinants of insulin sensitivity and secretion, we assessed whether the link between low birth weight and postnatal insulin resistance, regardless of gestational age, holds true (fig. 1) [12]. Sixty children born prematurely and of very low birth weight (20 born SGA and 40 born AGA), aged 5.7 ± 0.7 years, were evaluated by a short intravenous glucose tolerance test. The effects of current body mass index (BMI), birth weight SD score, postnatal growth rates and indicators of postnatal morbidity were evaluated. These children had been closely followed from birth to 7 years of age in a clinic in a well-defined area of Santiago, Chile. As a consequence of the strong geographical stratification in this city, this was an excellent indicator of socioeconomic homogeneity in our study group. A particular strength of this study was the analysis of early postnatal growth using instant growth rates that were independent of size at birth, which is essential if a separate assessment of the effects of birth weight and catch-up growth is desired. These children therefore had no endocrine bias. IUGR rather than low birth weight was found to be associated with increased fasting insulin levels. This link was independent of gestational age and other indicators of postnatal stress, such as early requirements for ventilatory and nutritional support. In addition, fasting and first-phase insulin secretion were related to instant postnatal growth velocity (which is independent of size at birth). This was in accordance with our previous observations. Interestingly, at this age, adiposity was the main determinant of insulin sensitivity and secretion.

Insulin is an important growth factor during infancy, and insulin secretion could be relevant for fat deposition and weight gain shortly after birth. This accelerated weight gain may in turn lead to the development of obesity in later life, thus contributing to development of insulin resistance. Our findings are in agreement with those of a prospective follow-up study of 385 preterm children at 9–12 years of age, with birth weights of less than 1,850 g. Anthropometric measurements and an oral glucose tolerance test were taken at birth and at 18 months and 7 years of age [13]. This study found that postload glucose concentrations were negatively correlated with birth weight independently of the length of gestation and postnatal growth. Fasting 32–33 split proinsulin concentrations and 30-min insulin concentrations were highest in children who showed the greatest increase in weight centile, regardless of gestational age. This suggests that fetal growth influences 30-min plasma glucose levels; however, in contrast, childhood weight gain was the most important factor influencing insulin concentrations.

Recently, a somewhat discordant finding was reported from the group of Hofman et al. [14]. They recruited 85 prepubertal children, aged 4–10 years, from an endocrine clinic; 50 had been born preterm (<32 weeks of gestation; 38 AGA, 12 SGA) and 35 had been born at term (22 AGA (controls), 13 SGA). Insulin sensitivity was measured with the use of an intravenous glucose tolerance test with paired insulin and glucose determinations. Interestingly, children who had been born prematurely had a reduction in insulin sensitivity compared with controls. The authors concluded, however, that children born small because of prematurity, regardless of their previous growth in utero, are also at risk of metabolic disease.

Hofman et al. comment very little on the interactions between size at birth and early postnatal growth in determining insulin sensitivity, which has been shown to be relevant in a number of recent studies [15, 16]. In this regard, it is noteworthy that children born SGA in the

study discussed above are rather short, probably because they had been recruited at a paediatric endocrinology clinic. This is in contrast to most population-based studies, which show that most (up to 90%) children born SGA, either at term or prematurely, experience complete catch-up growth before 4 years of age [17]. Therefore, we suggest caution should be exercised when extending these observations to other populations.

In epidemiological studies, the most common growth pattern related to disease risk in later life is the combination of low birth weight and subsequently becoming overweight or obese during childhood [18, 19]. Recently, experimental evidence for suppressed thermogenesis, favouring catch up in fat levels during catch-up growth, has been reported [20, 21]. This suppressed thermogenesis would lead to a redistribution of glucose from skeletal muscle to adipose tissue, linking catch-up growth and appearance of the metabolic syndrome in later life [21, 22]. These data are in accordance with data from Gale et al. [19], who showed that among men aged 70–75 years studied by dual-energy X-ray absorptiometry (DXA), low birth weight was associated with reduced lean tissue mass and greater body fat relative to current weight. Interestingly, a study of body composition in preterm infants, assessed by DXA, showed that fat mass and percentage fat mass increased substantially between discharge from hospital and 6 months of age, and values were similar to those in a control cohort of infants born at term. However, lean mass was reduced in the premature infants compared with that in the term reference infants at the same age [23]. It is also noteworthy that early postnatal growth in preterm infants has been negatively correlated with cord blood leptin [24].

Recently, a study by Bhargava et al. [25] has provided strong support to the hypothesis of an early-life origin of type 2 diabetes. They found that an early 'adiposity rebound' during childhood, even in the absence of overweight or obesity, is associated with a higher prevalence of impaired glucose tolerance and type 2 diabetes in young adults. However, their data do not rule out that an inappropriately high rate of weight and/or length gain may start even earlier. Detailed observations in contemporary cohorts indicate that BMI in prepubertal children is directly related to rates of weight gain during early infancy. This also seems to be the case for children of low birth weight, whose 'catch-up growth' seems to put them at risk of obesity and insulin resistance, despite being thinner than children of normal birth weight up to 3 years of age. In this regard, Singhal et al. [26] observed higher 32–33 split proinsulin concentrations in adolescents born preterm, aged 13–16 years, who had participated in randomized intervention trials of neonatal nutrition with a nutrient-enriched formula, compared with those receiving a low-nutrient formula.

## Conclusion

Identification of infants showing a rapid postnatal weight and/or length gain may help to focus preventive measures aimed at controlling the current epidemic of obesity and its complications. In Chile, the neonatal care group in charge of following up children of very low birth weight are carrying out a clinical trial to determine the influence of standard nutrition compared with a high-protein-enriched formula during the 1st year of life on growth and insulin sensitivity at 1 and 2 years of age. Until the results of this and other trials are available, we should be cautious in making recommendations.

## References


1 Farrag HM, Nawrath LM, Healey JE, Dorcus EJ, Rapoza RE, Oh W, Cowett RM: Persistent glucose production and greater peripheral sensitivity to insulin in the neonate vs. the adult. Am J Physiol 1997;272:E86–E93.

2 Rizza RA, Mandarino LJ, Gerich JE: Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am J Physiol 1981;240:E630–E639.

3 Battaglia FC, Thureen PJ: Nutrition of the fetus and premature infant. Nutrition 1997;13: 903–906.

4 Ng PC, Lam CW, Lee CH, Wong GW, Fok TF, Chan IH, Ma KC, Wong E: Leptin and metabolic hormones in preterm newborns. Arch Dis Child Fetal Neonatal Ed 2000;83:F198–F202.

5 Levitsky LL, Fisher DE, Paton JB, Delannoy CW: Fasting plasma levels of glucose, acetoacetate, D-beta-hydroxybutyrate, glycerol, and lactate in the baboon infant: correlation with cerebral uptake of substrates and oxygen. Pediatr Res 1977;11:298–302.

6 Simmons RA, Flozak AS, Ogata ES: Glucose regulates glut 1 function and expression in fetal rat lung and muscle in vitro. Endocrinology 1993;132:2312–2318.

7 Hoe FM, Thornton PS, Wanner LA, Steinkrauss L, Simmons RA, Stanley CA: Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinsim. J Pediatr 2006;148:207–212.

8 Leipala JA, Raivio KO, Sarnesto A, Panteleon A, Fellman V: Intrauterine growth restriction and postnatal steroid treatment effects on insulin sensitivity in preterm neonates. J Pediatr 2002;141:472–476.

9 Gray IP, Cooper PA, Cory BJ, Toman M, Crowther NJ: The intrauterine environment is a strong determinant of glucose tolerance during the neonatal period, even in prematurity. J Clin Endocrinol Metab 2002;87:4252–4256.
10 Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G, Ong KK, Dunger DB, Mericq MV: Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. J Clin Endocrinol Metab 2003;88:3645–3650.
11 Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993;36:62–67.
12 Bazaes RA, Alegria A, Pittaluga E, Avila A, Iniguez G, Mericq V: Determinants of insulin sensitivity and secretion in very-low-birthweight children. J Clin Endocrinol Metab 2004;89:1267–1272.
13 Fewtrell MS, Doherty C, Cole TJ, Stafford M, Hales CN, Lucas A: Effects of size at birth, gestational age and early growth in preterm infants on glucose and insulin concentrations at 9–12 years. Diabetologia 2000;43:714–717.
14 Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, Cutfield WS: Premature birth and later insulin resistance. N Engl J Med 2004;351:2179–2186.
15 Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C: Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 1999;48:2422–2429.
16 Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, Ness AR, Dunger DB: Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. Diabetologia 2004;47:1064–1070.
17 Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL: Children born small for gestational age: do they catch up? Pediatr Res 1995;38:267–271.
18 Ravelli GP, Stein ZA, Susser MW: Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–353.
19 Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C: Intrauterine programming of adult body composition. J Clin Endocrinol Metab 2001;86:267–272.
20 Crescenzo R, Samec S, Antic V, Rohner-Jeanrenaud F, Seydoux J, Montani JP, Dulloo AG: A role for suppressed thermogenesis favoring catch-up fat in the pathophysiology of catch-up growth. Diabetes 2003;52:1090–1097.
21 Dulloo AG: Regulation of fat storage via suppressed thermogenesis: a thrifty phenotype that predisposes individuals with catch-up growth to insulin resistance and obesity. Horm Res 2006;65(suppl 3):90–97.
22 Cettour-Rose P, Samec S, Russell AP, Summermatter S, Mainieri D, Carrillo-Theander C, Montani JP, Seydoux J, Rohner-Jeanrenaud F, Dulloo AG: Redistribution of glucose from skeletal muscle to adipose tissue during catch-up fat: a link between catch-up growth and later metabolic syndrome. Diabetes 2005;54:751–756.
23 Cooke RJ, Rawlings DJ, McCormick K, Griffin IJ, Faulkner K, Wells JC, Smith JS, Robinson SJ: Body composition of preterm infants during infancy. Arch Dis Child Fetal Neonatal Ed 1999;80:F188–F191.
24 Fonseca VM, Sichieri R, Moreira ME, Moura AS: Early postnatal growth in preterm infants and cord blood leptin. J Perinatol 2004;24:751–756.
25 Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, Biswas SK, Ramji S, Prabhakaran D, Reddy KS: Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865–875.
26 Singhal A, Fewtrell M, Cole TJ, Lucas A: Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089–1097.