Perinatal energy metabolism with reference to IUGR & SGA: Studies in pregnant women & newborn infants

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Glucose is the most important fetal energy substrate. During the third trimester increased maternal glucose production and insulin resistance improves fetal glucose availability. Maternal malnutrition, chronic disease and/or placental dysfunction can disturb glucose delivery, resulting in intrauterine growth restriction (IUGR) and an infant born small for gestational age (SGA). Hypoglycaemia is a problem frequently occurring in infants born SGA; they are also at long-term risk of developing insulin resistance. In the studies presented, energy substrate production was investigated using stable isotope dilution technique, in normal pregnancies and pregnancies complicated by intrauterine growth restriction (IUGR). In addition energy substrate production in infants born SGA was studied on their first day of life. We found that late pregnancy was associated with an almost twofold increase in rate of lipolysis. This provides substrates for maternal energy metabolism, sparing glucose for the fetus. Even though glucose production was comparable in the two groups of pregnant women, those with IUGR had a lower rate of lipolysis. A reduced supply of energy substrates could be one factor underlying IUGR. In spite of the insulin resistance of late gestation, insulin still had a regulatory role in energy substrate production in the women with normal pregnancies, but not in those with IUGR. Although infants born SGA have limited energy stores, we demonstrated that they are capable of both lipolysis and glucose production. Data on insulin and IGFBP-1 in the SGA infants indicate that insulin sensitivity is increased peripherally but reduced in the liver.

Key words Gluconeogenesis - glucose - glycerol - intrauterine growth restriction - lipolysis - newborn infant - stable isotope

Introduction

Fetal growth is dependent upon continuous transfer of oxygen and nutrients cross the placenta from the mother. Maternal disease and malnutrition as well as impaired placental function can disturb nutrient availability and attenuate the growth of the fetus. During pregnancy there are several adaptive mechanisms providing substrates for energy production. In late gestation, there is an accelerating fetal weight gain and the pregnant woman adjusts her metabolism to meet this increased demand.

The postnatal adaptation in the newborn infant involves activation of several metabolic pathways. After birth the newborn infant must produce its own glucose, primarily for the brain. Fatty acids from lipolysis are also important energy substrates. Hypoglycaemia can be a frequently occurring problem in newborn infants being small for gestational age (SGA).
The last decades much interest has been focused on long-term effects of fetal growth restriction. The hypothesis of “fetal programming” states that the fetus adapts to limited nutritional support with metabolic consequences later in life. Some of these metabolic changes may already occur at early school age. However, there is a lack of information about the metabolic situation of the newborn SGA infant.

In the studies reviewed we measured energy substrate production and its hormonal regulation in pregnant women with normal size and growth restricted fetuses as well as in newborn infants born SGA.

Measurements of energy substrate production

The rate of lipolysis and hepatic glucose production, in the studies reviewed, were measured with stable isotope dilution technique. Isotopes are chemically identical atoms with different numbers of neutrons, resulting in changed atomic weights. Stable isotopes are not radioactive and occur naturally in small amounts. The tracers used in pregnant women were [6,6-$^2$H$_2$]-glucose and [1,1,2,3,3-$^2$H$_5$]-glycerol. In the study on infants born SGA the tracers used were [6,6-$^2$H$_2$]-glucose and [2-$^{13}$C]-glycerol.

By infusing a known amount of stable isotope labelled glucose and glycerol (reflecting lipolysis) after achieving approximate steady state in the circulation, it is possible to calculate the turnover rate of these substrates. The isotopic enrichments in the samples are analysed in a mass spectrometer/gas chromatograph. The advantage of this methodology is that only small sample volumes are needed enabling studies in newborn infants. The studies were approved by the Human Ethics Committee of the Medical Faculty of the University of Uppsala. Informed and written consent were obtained from the pregnant women and the parents of the infants.

Normal pregnancy

Efficient maternal energy production is important to adequately support fetal growth and weight gain in preparing the metabolic adaptation of the newborn infant after birth.

Glucose is the most important energy substrate and the fetal brain is dependent on glucose as source of energy. In late gestation maternal glucose production increases by 16-30 per cent in order to meet the needs of the fetus and placenta. In line with these data we could show increased glucose production rate (GPR) (13.2±1.5 µmol/kg/min) in women with normal pregnancies compared to reported data for non-pregnant women (10 µmol/kg/min). We found an inverse correlation between maternal anthropometric data and the rate of glucose production (height $r=-0.80$, $P<0.05$; pre-pregnancy weight $r=-0.72$, $P<0.05$), suggesting that the requirements of the brain and the feto-placental unit, and not primarily maternal size, determines glucose turnover at rest.

The insulin resistance in late pregnancy increases the glucose availability in the maternal circulation by reduced peripheral glucose uptake, increased glycogenolysis and gluconeogenesis. In the fasting situation, ketone bodies are formed by β-oxidation of non-esterified fatty acids (NEFA). The ketone bodies can be used both as energy substrates and for lipid synthesis by the foetus.

Transport of energy substrates cross the placenta is dependent on the blood flow in the uterine artery, the maternal-fetal gradient of substrates, the area of the maternal-fetal interface and the density of specific transport molecules (Fig. 1). Glucose is transported by facilitated diffusion via the insulin-independent glucose transporter 1 (GLUT1). Specific transport proteins actively transports amino acids, resulting in a fetal-maternal gradient. There is a limited transport of lipids across the placenta. Most NEFA cross the placenta by simple diffusion, but there is an active transport of essential fatty acids via fatty acid binding proteins (FABPs). In early gestation fetal lipids come from maternal NEFA, but in late pregnancy most of the fetal fat stores are synthesised from glucose. The transport

![Fig. 1. Energy substrates transported to and deposited in the foetus](image-url)
of glycerol (a product of lipolysis) is also limited, but can instead be used as a substrate for gluconeogenesis in the mother\textsuperscript{16}.

Maternal lipolysis is enhanced in late pregnancy by the hormones underlying insulin resistance\textsuperscript{21}. During fasting in the third trimester the change from the use of carbohydrates to lipids is more rapid when comparing with non-pregnant women\textsuperscript{22}. Additional substrates for maternal energy metabolism is provided by the increased rate of lipolysis, saving glucose and amino acids for the fetus\textsuperscript{23}. We could show an almost 50 per cent increase in the rate of lipolysis in women with normal pregnancies (3.06±0.66 \(\mu\)mol/kg/min)\textsuperscript{6}, as compared to reported data for non-pregnant women (1.65±0.6 \(\mu\)mol/kg/min)\textsuperscript{13}. The increased lipolysis in the women with normal pregnancies probably provides substrates for maternal energy metabolism. The energy from lipolysis supports gluconeogenesis, also indicated by the positive correlation between maternal glycerol production and GPR (\(r=0.75, P=0.033\)) (Fig.2) in our study on healthy women with normal pregnancies. The fetus can benefit from this de-novo synthesis of glucose.

Data from healthy pregnant women show an inverse correlation between levels of insulin and glucose (\(r = -0.78, P=0.021\)) as well as glycerol production (\(r = -0.85, P=0.008\)). Indicating that insulin still have a regulatory role in spite the insulin resistance of late pregnancy.

**Intrauterine growth restriction**

The incidence of IUGR is about 4-8 per cent of newborn infants in industrialised countries and 6-30 per cent in developing countries, depending on what population being assessed. One third of all infants weighing less than 2500 g are considered to earlier have been intrauterine growth restricted\textsuperscript{24}.

Maternal malnutrition is the most common factor causing IUGR worldwide, but there are other factors that can explain this condition (Table). In 40 per cent of the cases there is no apparent underlying factor\textsuperscript{25}. Intrauterine growth restriction is associated with a considerable risk of fetal and neonatal mortality and morbidity\textsuperscript{26,27}, including prenatal still-birth and intrapartum asphyxia, with later neurological sequelae\textsuperscript{28}.

In our study assessing women with pregnancies complicated by IUGR,\textsuperscript{7} the rate of lipolysis (2.36±0.58 \(\mu\)mol/kg/min) was decreased in comparison with that in normal pregnancies (3.06±0.66 \(\mu\)mol/kg/min)\textsuperscript{6}. Although the number of women was limited (normal pregnancy n=8 and IUGR n=10), both groups were uniform in that all were healthy and non-smoking. Reduced maternal lipolysis in IUGR might influence the total energy substrate availability and reducing the total amount of glucose transferred to the fetus.

There was no difference between the two groups of pregnant women in studies performed in our group with regard to fasting blood glucose levels and rates of glucose production, indicating that impaired maternal glucose production does not seem to be a factor underlying intrauterine growth restriction.

There was an inverse correlation between levels of insulin and rates of glucose production and lipolysis

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**Table.** Factors underlying fetal growth restriction

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<td>Hypoxaemia (high altitude)</td>
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<td>Placental dysfunction (pre-eclampsia, infarctions, bleeding, reduced area)</td>
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in the women with normal pregnancies, indicating a regulatory role for insulin, in spite of the reduced insulin sensitivity in late pregnancy. In contrast in women with IUGR we did not find any correlation between insulin and rates of energy substrate production, nor between lipolysis and glucose production. This indicates an altered regulation of energy substrate production in this group of pregnant women.

**Infants born SGA**

During the first days of life infants born SGA are at increased risk of developing hypoglycaemia. Small energy stores, a high brain:body weight ratio, delayed maturation of the gluconeogenic pathways and/or neonatal hyperinsulinaemia are possible explanatory factors.

There is only limited data available on energy substrate production, particularly on lipolysis and gluconeogenesis in newborn SGA infants. In a study on infants born SGA, we could show that their rates of hepatic glucose production were in the lower normal range (21.1±6.1 µmol/kg/min), when comparing with data from appropriate for gestational age (AGA) infants (ranging between 19.6 - 33.7 µmol/kg/min). This is in line with earlier data in this particular group of infants (23.6 and 23.1 µmol/kg/min). The SGA infants were divided into two groups, one group being preterm were given additional glucose and the other group was more mature without glucose infusion, the groups only differed in rate of appearance of glucose and not in GPR. Although the number of infants was small, the results suggest that the infants in fact needed extra energy support.

Lipolysis contributes to the energy requirements during the immediate postnatal period. The rate of lipolysis varies considerably in earlier studies on preterm and term AGA and SGA infants. Lipolysis in our study (5.6 µmol±1.6 µmol/kg/min), in the infants born SGA was lower than in most studied term infants (mean 4.4; 8.7 and 9.5 µmol/kg/min). This is not surprising considering the limited amount of stored fat in this group. Moreover, in the SGA infants birth weight correlated with the rate of glycerol production, indicating that lipolysis depends on the amount of stored fat (Fig. 3).

In the infants born SGA, in our study, approximately half of the glycerol was converted to glucose and this contributed to 8 per cent of the total GPR. This level of gluconeogenesis from glycerol is in the same range as in most studied AGA infants. There was a higher conversion of glycerol to glucose in SGA infants without glucose infusion, indicating that glycerol is an important gluconeogenic substrate under these conditions.

There is a long-term risk of reduced insulin sensitivity, a risk factor for development of type 2 diabetes mellitus, in infants born SGA. This has much increased the interest in the regulation of energy metabolism in infancy and childhood in this group of children. The concept of “fetal programming” refers to an adaptation to reduced nutritional support during fetal life with life-long consequences.

The data concerning hormonal regulation of energy substrate production in the newborn infant born SGA is limited. The levels of insulin in our infants (6.7±1.7 mU/l) were comparable with those of a large cohort of SGA infants investigated 48 hours postnatally (4.5 mU/l), but lower than levels reported for AGA infants (8.9 mU/l) in the same study. This is in contrast with earlier results suggesting that hyperinsulinaemia may occur already at birth. There was no relationship between the level of insulin or the insulin/gluconucous ratio and GPR in our infants is in agreement with earlier data, the authors proposed that the neonatal hepatocyte may be insensitive to insulin. Reduced hepatic insulin sensitivity is also supported by the increased IGFBP1 levels as well as IGFBP1/insulin ratios found in SGA infants in earlier studies. The decreased hepatic insulin sensitivity was not associated with a corresponding increase in GPR. This may be
due to reduced substrate availability and/or delayed activation of enzymes in gluconeogenesis.

The glucose/insulin ratio in these infants are compatible with the occurrence of increased neonatal peripheral insulin sensitivity in infants born SGA. This increase indicates that insulin resistance does not occur until later in life.

Conclusion

This article addresses questions concerning perinatal energy substrate production in normal pregnancy and in pregnancies complicated by IUGR, as well as in newborn infants born SGA.

With the use of stable isotope dilution technique it is possible to perform studies on energy substrate kinetics from small sample volumes, which makes it particularly suitable for studies in newborn infants.

In normal pregnancy glucose production was increased by almost 30 per cent and lipolysis almost doubled in late gestation compared to reported data from non-pregnant women. Lipolysis was reduced by 30 per cent in women with IUGR compared to women with normal pregnancies, but levels of glucose production were comparable. Reduced supply of energy substrates could be one factor underlying IUGR. In women with normal pregnancies insulin had a regulatory role on energy substrate kinetics in spite of the insulin resistance seen in late pregnancy, no such effect of insulin were seen in women with IUGR.

Even if infants born SGA have limited energy stores, we demonstrated that they were capable of lipolysis as well as glucose production. Data on insulin and IGFBP-1 in the SGA infants indicate that insulin sensitivity is increased peripherally but reduced in the liver.

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