Adipose Tissue Development “in Utero”

Relationships between Some Nutritional and Hormonal Factors and Body Fat Mass Enlargement in Newborns

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Summary. Some metabolic and hormonal variables, thought to affect adipose tissue development “in utero” were studied in a group of 50 presumably healthy mothers and in their full-term infants. No sex-related differences were observed at birth in skinfold thickness, body fat mass, fat cell volume or fat cell number. Body fat mass in newborns was significantly correlated to fat cell size ($r = 0.75$; $p < 0.001$), but not to fat cell number. Weight gain during pregnancy but not prepregnancy weight was correlated to fat cell volume in the newborn ($r = 0.67$; $p < 0.001$) and to body fat mass ($r = 0.66$; $p < 0.001$). Maternal placental lactogen levels correlated to decreased glucose tolerance in the mothers ($r = 0.62$; $p < 0.001$), as well as to body fat mass ($r = 0.61$; $p < 0.001$) and fat cell size ($r = 0.58$; $p < 0.001$) in newborns. Neonatal plasma insulin levels in addition correlated with body fat mass ($r = 0.39$; $p < 0.05$) and fat cell weight ($r = 0.69$; $p < 0.001$) of the neonate. Placental NEFA transfer could be demonstrated, but there was no correlation between maternal plasma NEFA levels and neonatal body fat mass or fat cell weight. Similarly, maternal insulin and growth hormone levels were not correlated with neonatal body fat mass or with fat cell size or number. Thus the nutritional and hormonal factors considered do not appear to be involved in fat cell multiplication. During intrauterine life, in full-term infants of presumably healthy mothers, fat mass expansion seems to occur almost exclusively by means of fat cell hypertrophy.

Key words: Adipose tissue, body fat mass, fat cell size, fat cell number, human placental lactogen, glucose tolerance, insulin, growth hormone, free fatty acids.

One of the most striking changes in fetal body composition during the last trimester of gestation is an increase in triglyceride content, due to differentiation of adipose tissue. Thus already by the 30th week of intrauterine life, adipose tissue is sensitive to stimuli inducing cellular proliferation [1]. Perinatally, the number and volume of fat cells increase rapidly under nutritional and hormonal stimuli [2, 3, 4, 5]. Several studies have demonstrated that in childhood obesity there is an increase in both fat cell size and number [6, 7].

Hypercellularity of adipose tissue at birth, therefore seems to represent a predisposing factor towards obesity. On the other hand, some maternal conditions, such as reduced glucose tolerance, obesity, or excessive weight gain during pregnancy are often associated with an increase in neonatal weight or with fetal macrosomy [8, 9, 10]. In newborn infants of diabetic mothers an enlargement of body fat mass due probably to fetal hyperglycaemia and hyperinsulinaemia has been observed [11]. Theoretically, other substrates could regulate adipose tissue development “in utero” by inducing an enlargement of adipose cells or an increase in fat cell number (Fig. 1). The aim of the present study was to evaluate the development of adipose tissue in the full-term newborn in relation to hormonal and metabolic variables in the neonate itself and in the mother.

Materials and Methods

Mothers

Fifty presumably normal, randomly selected, pregnant women and their respective infants born by normal vaginal delivery at term of uneventful pregnancies were studied. Gestational age, determined from menstrual history, ranged between 38 and 40 weeks. None of

the mothers received any metabolically active drug or restricted diets. None became hypertensive during the pregnancy.

During the 34th and 35th weeks of pregnancy, venous blood specimens were collected after an overnight fast in the mothers for blood glucose, plasma free fatty acids (NEFA) [12], insulin (IRI) [13], growth hormone (HGH) [14] and placental lactogen (HPL) [15] determination. The values reported for each mother represent the mean of at least 3 determinations performed at intervals of 3–4 days.

All the mothers underwent, after an overnight fast, a 100 g oral glucose tolerance test (OGTT) at the 34th week of pregnancy. Venous blood samples were collected at 0, 30, 60, 90, 120, 180, 240 and 300 min for blood glucose and plasma IRI determination. No dietary preparation was carried out in the days before the test. Glucose tolerance and insulin release of each subject were expressed as areas in square millimeters of blood glucose (BG area) and plasma insulin (IRI area) curves, plotted on millimetric paper (1 mm = 0.1 min on abscissa, 0.1 mg of glucose or 0.1 unit of IRI on ordinate).

Body weight gain during pregnancy was recorded. The ideal weight gain for each mother was calculated on the basis of the individual ideal body weight [16]. Skinfold thickness measurements were performed on the subscapular and triceps regions (Harpender Caliper) at the time of delivery.

The mothers were grouped on the basis of glucose tolerance, prepregnancy weight, and weight gain during pregnancy according to the following criteria:

a) *Carbohydrate Tolerance*: Mothers with a blood glucose area during OGTT greater than 310 (corresponding to a "borderline" curve area) were placed in the decreased glucose tolerance group.

b) *Prepregnancy Weight*: Mothers whose weight before pregnancy did not exceed 10% over their ideal body weight [17] were considered normal, while those whose body weight before pregnancy exceeded 10% of their IBW were considered overweight. None of these mothers were on caloric-restricted diets.

c) *Weight Gain during Pregnancy*: Mothers, who at term did not exceed 20% of the ideal body weight increase were considered normal. Those showing a weight gain at term exceeding 20% were included in the excess weight gain group.

Neonates

In each neonate skinfold thickness was measured in the crural, subcostal, subscapular and triceps regions (Harpender Caliper) [18]. Following written parental consent, within 8 hours of birth a needle microbiopsy of fat tissue (less than 1 mg per sample), at the upper-outer quadrant of the buttocks was performed, the skin surface being previously anaesthetized with anaesthetic spray. A butterfly needle gauge 19 was used for biopsies. Fat cell diameter was determined in frozen-cut slices of adipose tissue [19]. Body fat mass was calculated from anthropometric measurements using the following formula [20]:

$$\text{BFM} = 0.9 (A + 2B + 2C)$$

A, B and C represent the volume of the cylindrical shell covering respectively trunk, upper limb and lower limb, the factor 0.9 being the density of human fat.

An indirect and approximate estimate of fat cell number was obtained for each neonate from the ratio between fat mass and fat cell weight.

Four hours following birth, venous blood specimens were collected in neonates for blood glucose, plasma IRI and NEFA determination. In 20 newborn infants who received immediately after

birth treatment known to have metabolic effects (eg.: steroids, glucose infusion, etc.) these variables were not included in the correlation studies.

Placental Non-esterified Fatty Acid Transport

To evaluate placental transfer, plasma NEFA were determined at delivery in venous blood samples in a separate group of 15 untreated mothers and in cord blood-samples of their respective newborn infants. Blood samples were collected in cooled vials, immediately transferred to the laboratory for centrifugation. Plasma was stored at -20°C for a maximum of 2 days.

Statistical analyses were carried out using the Student's "t" test for comparison of the means and the simple linear regression equation for correlations.

Results

Mean values of the anthropometric, metabolic and hormonal variables studied in mothers and neonates are shown in Tables 1 and 2. No sex-related differences were observed in birth weight, body fat mass, skinfold thickness and fat cell size or number in neonates (Table 2). A significant positive correlation was found between fat cell weight and body weight ($r = 0.58$; $p < 0.001$), skinfold thickness ($r = 0.73$; $p < 0.001$) and body fat mass ($r = 0.75$; $p < 0.001$) in the neonates. No relationship was found, however, between these variables and fat cell number.

Maternal Prepregnancy Weight and Adipose Tissue Development in Neonates

At birth, body weight, body fat mass, fat cell number and fat cell size were not significantly greater in infants born to overweight mothers. Blood glucose area, IRI area and plasma HPL values were not significantly different in the overweight and normal mothers.

Nevertheless, maternal prepregnancy overweight was correlated to neonatal birth weight ($r = 0.31$; $p < 0.05$), body fat mass ($r = 0.33$; $p < 0.05$) and to fat cell weight ($r = 0.37$; $p < 0.01$). A correlation was also observed between maternal skinfold thickness and fat cell weight in the neonate ($r = 0.34$; $p < 0.05$).

Maternal Weight Gain during Pregnancy and Adipose Tissue Development in Newborns

Mothers with excessive weight gain during pregnancy had significantly increased insulin release during the OGTT (Table 3). Body weight, body fat mass, sum of skinfold thickness and fat cell weight were significantly higher in their infants. Furthermore weight gain of the mothers during pregnancy was signifi-

Table 1. Anthropometric, metabolic and hormonal variables in 50 apparently healthy, randomly selected pregnant women (mean $\pm$ SEM)

Age (yrs)	Height (cm)	Prepreg- nant body weight (kg)	Prepreg- nant % ideal body weight	Body weight gain (kg)	Skinfold thickness ^a			Blood glu- cose (mg/dl)	Plasma IRI (μ U/ml)	OGTT		Plasma NEFA μ mol/l	Plasma HPL (μ g/ml)
					T (mm)	SS (mm)	Σ (mm)			Blood glucose area	IRI area		
28.2 ± 0.9	161 ± 0.8	63.3 ± 1.5	15.5 ± 2.4	11.4 ± 0.7	18.5 ± 0.9	20.3 ± 0.9	38.2 ± 1.7	84 ± 2.0	5.9 ± 0.9	327 ± 11	204 ± 23	325 ± 21	7.1 ± 1.2

^a T = Triceps SS = Subscapular Σ = Sum of T and SS

Table 2. Body weight and length at birth, skinfold thickness and indices of adipose tissue development in newborn infants (mean $\pm$ SEM)

n	Body weight kg	Length (cm)	Skinfold thickness ^a					Body fat mass (g)	Fat cell weight (μ g)	Fat cell number ($\times 10^9$)	Blood glucose (mg/dl)	NEFA (μ mol/l)	IRI (μ U/ml)
			T (mm)	SC (mm)	SS (mm)	C (mm)	Σ (mm)						
50	3.24 ± 0.1	49.1 ± 0.4	4.2 ± 0.2	3.9 ± 0.1	5.0 ± 0.2	6.3 ± 0.3	19.4 ± 0.6	439 ± 22	0.24 ± 0.03	2.12 ± 0.3	64 ± 4.0	551 ± 85	8.6 ± 2.4

^a T = Triceps SC = Subcostal SS = Subscapular C = Crural Σ = sum of T, SC, SS, C values

Table 3. Adipose tissue development in newborn infants in relation to the maternal weight gain during pregnancy (mean $\pm$ SEM)

	n	Mothers				Neonates						
		Prepreg- nancy body weight (kg)	Weight gain (kg)	Blood glu- cose area	Plasma IRI area	Plasma HPL (μ g/ml)	Body weight at birth (kg)	Length (cm)	Body fat mass (g)	Sum of skinfold thickness (mm)	Fat cell weight (μ g)	Fat cell number ($\times 10^9$)
Normal weight gain	27	62.7 ± 2.6	8.7 ± 0.5	315 ± 13	163 ± 15	6.3 ± 1.1	3.04 ± 0.09	48.8 ± 0.8	397 ± 21	18.3 ± 0.7	0.20 ± 0.02	2.3 ± 0.3
Excessive weight gain	23	60.6 ± 3.8	16.5 ± 1.4	306 ± 14	277 ± 47	7.7 ± 1.5	3.45 ± 0.17	49.6 ± 0.5	509 ± 50	21.7 ± 1.3	0.35 ± 0.06	2.0 0.3
p		NS	<0.001	NS	<0.05	NS	<0.05	NS	<0.05	<0.05	<0.05	NS

cantly correlated to body weight at birth ($r = 0.53$; $p < 0.001$) body fat mass ($r = 0.66$; $p < 0.001$) and fat cell weight ($r = 0.67$; $p < 0.001$) in the neonates. No correlation was observed between weight gain during pregnancy and fat cell number in the neonate.

Maternal Glucose Tolerance and Insulin Release during OGTT, Neonatal Glucose and Insulin Levels and Adipose Tissue Development in Newborns

No significant differences in body fat mass, in fat cell weight or number were observed in neonates of mothers with reduced carbohydrate tolerance. Blood glucose area during OGTT correlates positively with neonatal body fat mass ($r = 0.34$; $p < 0.05$) but not to fat cell weight or number. No statistically significant correlations were observed between insulin area during the OGTT and neonatal body fat mass, fat cell weight or fat cell number.

Maternal Plasma HPL and HGH Levels and Adipose Tissue Development in Newborns

Maternal plasma HPL levels were significantly correlated with neonatal body weight, body fat mass and fat cell weight, but not with the fat cell number. A significant correlation was also observed between plasma HPL and blood glucose area following oral glucose loading (Table 4). No significant correlation was found between maternal plasma HGH levels and any of the variables measured.

Maternal and Neonatal Plasma NEFA Levels

No correlation was found between maternal or neonatal plasma NEFA values and neonatal body weight, body fat mass, fat cell size or fat cell number.

Plasma NEFA values at delivery were constantly higher in the mothers ($466 \pm 38 \mu\text{mol/l}$) than in the

Table 4. Relationships between plasma HPL values in the mothers and glucose tolerance or insulin release in the mothers and indices of adipose tissue development in newborn infants

X	y	Regression equation	Correlation coefficient (r)	P
<i>Maternal</i>				
Plasma HPL	Blood glucose area	$y = 6.97x + 261$	0.62	<0.001
Plasma HPL	Plasma IRI area	$y = 1.41x + 16.2$	0.31	<0.05
<i>Neonatal</i>				
Plasma HPL	Body weight at birth	$y = 0.04x + 2.78$	0.54	<0.001
Plasma HPL	Body fat mass	$y = 12.20x + 325$	0.61	<0.001
Plasma HPL	Fat cell weight	$y = 0.20x + 0.14$	0.58	<0.001
Plasma HPL	Fat cell number	$y = 0.07x + 2.97$	0.18	NS

Fig. 1. Hormonal and metabolic factors in the maternal-feto-placental unit theoretically implicated in the regulation of adipose tissue development during intrauterine life

neonates ($308 \pm 26 \mu\text{mol/l}$) with a mean gradient of $160 \pm 12 \mu\text{mol/l}$. A statistically significant correlation resulted between maternal and neonatal plasma NEFA values at birth ($r = 0.56$; $p < 0.05$).

Discussion

Body fat mass varies markedly in full term infants. The fluctuations seem to be largely related to variations in fat cell size.

At birth no sex-related differences in body fat mass, in skinfold thickness of different sites and in adipose tissue cellularity were observed. It would seem therefore that the marked differentiation between females and males in cellularity and in regional distribution of adipose tissue [21, 22, 23] takes place later in childhood.

It has been reported that infants of obese mothers are heavier at birth [24, 25]. This may lead to the

assumption that these infants are born with a greater body fat mass. In the present study truly obese women were not included. Nevertheless body fat mass, fat cell size, and fat cell number in neonates born to overweight mothers were not significantly different from those born to normal mothers. A different caloric intake during pregnancy could be responsible for a different growth of adipose tissue "in utero" in the newborn. Even if water retention in some mother could be partially responsible for weight increase, in normal pregnancies excessive weight gain mainly depends on increased caloric intake. A close relationship between maternal weight gain during pregnancy and neonatal body weight has been reported [26, 27]. In the same manner, adipose tissue development seems to be related to weight gain during pregnancy. In fact, body fat mass, skinfold thickness and fat cell volume were significantly greater in the neonates of mothers with excessive weight gain and a statistically significant positive correlation was observed between neonatal body fat mass or fat cell size and maternal weight gain during pregnancy. Excessive weight gain, therefore, seems to be one of the most important factors responsible for fat cell hypertrophy and thus for expansion of the neonatal fat mass.

Fetal macrosomia has been frequently reported in children of gestational diabetic mothers [8, 9, 10, 28]. A tendency towards hypercellularity of adipose tissue has been described in rats born to diabetic mothers [29] but not confirmed in human subjects [11, 29]. In the present study no correlations were found between maternal fasting insulin values or insulin response to OGTT and neonatal body fat mass or fat cell size. It seems, therefore, that maternal insulin does not directly influence fat mass development "in utero". This can be explained by the fact that maternal insulin cannot cross the placental barrier [30, 31, 32, 33].

It has been observed that fetal lipids have a higher percentage of C₁₆ fatty acids, preferentially formed by lipogenesis from glucose [34]. In the present study statistically significant correlations between neonatal insulin levels and body fat mass or fat cell size have been observed. This supports the hypothesis that "in utero", as in adulthood [35], glucose and insulin represent primary factors directly regulating triglyceride synthesis and storage in adipocytes.

It is known that fuel availability to the fetus is largely conditioned by maternal levels of energy substrates [36, 37, 38], prevalently regulated by HPL (Fig. 1). This hormone induces maternal hyperglycaemia by reducing peripheral glucose utilization and by increasing gluconeogenesis [39, 40, 41]. At the same time by stimulating lipolysis [39, 42] HPL augments circulating glycerol and NEFA levels and thus the splanchnic production of ketone body. All of these substrates could represent a source for triglyceride synthesis in adipose tissue, particularly in situations of enhanced lipid mobilisation, i. e. fasting state or insulin dependent diabetes. The positive, statistically significant, correlation between plasma HPL values and blood glucose area after oral glucose loading observed confirms the diabetogenic effect of this hormone. The decrease in glucose utilization in mothers induced by HPL, would ensure a steady supply of glucose for the fetus. Furthermore, the correlations between maternal HPL levels and neonatal body fat mass or fat cell size suggest that this hormone may affect triglyceride synthesis and storage in fetal fat cells during intrauterine life. HPL could carry out this effect by enhancing glucose availability to the fetus which, in turn, stimulates higher insulin release. Indeed, by the 30th week of gestation the fetal pancreas can modulate insulin release in response to circulating glucose levels [43, 44, 45].

The relationship observed between NEFA levels in mothers and in neonates at delivery, confirms the placental transfer of this substrate [46, 47, 48]. It has been suggested that maternal NEFA might play a primary role in regulating fetal development [49]. Theoretically, circulating NEFA may constitute a substrate for triglyceride synthesis in fetal fat tissue. In our subjects, however, there was no correlation between maternal NEFA levels and any index of fat tissue development in the neonate. NEFA therefore, do not seem to have in normal pregnancies a relevant role in regulating triglyceride content in fetal adipose tissue. In infants born to presumably healthy, casually selected mothers, the variation in volume of the fat cells largely accounts for fat mass expansion. Calculations of fat cell number in newborns with available methodology have serious shortcomings,

because only fat filled adipocytes can be measured. Nevertheless, it does not seem that the hormonal and metabolic factors considered affect adipose tissue cellularity during intrauterine life. It might be that if pregnant women with more pronounced deviations in terms of prepregnancy obesity, weight gain or carbohydrate intolerance were studied, more striking influences on adipose tissue cellularity would be found.

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