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Sonographic Measurements of Subcutaneous Fetal Fat in Pregnancies Complicated by Gestational Diabetes and in Normal Pregnancies

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Aim. To compare sonographic measurements of fetal fat tissue in pregnancies complicated by gestational diabetes (GD), undergoing either a diet only or a combined diet and insulin treatment, to those obtained in pregnancies with a normal glucose challenge test.

Methods. Forty-five singleton pregnancies complicated by GD but free of any other maternal disease known to affect fetal growth were recruited. GD was diagnosed by a 3-hour OGTT, and treatment was differentiated according to the glycemic profile. GD mothers were stratified into two treatment groups: glycemic profile normalized by diet only treatment (n=16), or by combined diet and insulin treatment (n=29). Fetal biometry and subcutaneous fat tissue thickness of the anterior abdominal wall were sonographically evaluated at the time of diagnosis and every 4 weeks afterwards in both GD and normal glucose challenge test group (n=25).

Results. No differences were found in neonatal outcomes between combined diet and insulin treatment group and normal cases, whereas neonatal weight showed a statistically significant difference between diet only treatment group and normal population. Abdominal circumference was similar in fetuses from GD mothers and normal fetuses, but there was a difference in the fetal fat tissue thickness at the time of diagnosis.

Conclusion. Increased fetal fat tissue thickness in GD at recruitment and its growth rate reduction during an adequate treatment may be a new criterion for direct estimation of fetal metabolic status instead of the traditional indirect evaluation based on maternal glucose concentrations.

Key words: *adipose tissue; diabetes, gestational; fetal monitoring; glucose tolerance test; insulin; ultrasonography*

Gestational diabetes represents an important pregnancy disease, because of both its high prevalence and the possible fetal and maternal complications. The most relevant fetal consequence of maternal gestational diabetes is excessive or accelerated growth of the fetus, which results in macrosomia, defined as either a fetal abdominal circumference above the 90th percentile or a birth weight above 4,000 grams (1). The incidence of fetal and neonatal macrosomia is 8% and 26% among non-diabetic and diabetic pregnancies, respectively (2). Despite the recent clinical progress in the management of gestational diabetes, the likelihood of fetal macrosomia remains significantly higher in diabetic than in normal pregnancies (2).

During the first trimester of gestation, embryonal growth velocity is very high, but 95% of fetal weight at term has to be accumulated during the second half of pregnancy (3). Moreover, early in gestation fetal growth is mainly under genetic control, whereas in the second and third trimesters different factors play a role in determining the features of fetal auxology. All these factors may affect fetal growth by influencing the transport of nutrients and oxygen from maternal blood through the placenta into the fetal circulation. In diabetic mothers, an increase in the plasma levels of glucose, free fatty acids, triglycerides, and several amino acids has been observed (4). There is a large body of literature published on the power of ultrasound measurements to predict macrosomia. These studies have demonstrated that the increase in fetal insulin-dependent tissue growth rate is better estimated by the sonographic measurement of fetal abdominal circumference than of biparietal diameter, which is a non insulin-dependent

tissue (5-11). Adipose tissue thickness and skinfold thickness are greater in newborns of mothers with gestational diabetes than of mothers with normal maternal glucose metabolism. The excessive fetal growth is due to the fetal hyperinsulinism determined by the association of maternal and fetal hyperglycemia. Despite the fact that a direct correlation between glucose blood values and fetal macrosomia has been demonstrated, the real cut-off levels of maternal glucose concentrations which would prevent excessive fetal growth are not known. Moreover, significantly higher C-peptide cord blood concentrations have been found (12) in non-diabetic pregnancies with fetal macrosomia. These findings could suggest that maternal euglycemia is not sufficient to prevent fetal macrosomia.

The ultrasonographic determination of abdominal circumference is able to predict 78% of macrosomic fetuses (13). This measurement has been used to identify cases at risk for fetal macrosomia among gestational diabetic mothers (14). In the recent years, lean and fat fetal body composition has been evaluated by ultrasound (15,16). The ratio between these two components can suggest fetal hyperinsulinism even if the mother is euglycemic. These studies have demonstrated that growth of lean body mass reaches steady state near term, whereas the fetal fat body mass increases exponentially during the third trimester, if correlated with neonatal weight variations.

Our specific aim was to compare sonographic measurements of fetal fat tissue in pregnancies complicated by gestational diabetes and undergoing either a diet only or a combined diet and insulin treatment, to those obtained in pregnancies with a normal glucose challenge test.

Subjects and Methods

This study was performed at the Department of Obstetrics and Gynecology of the San Paolo Hospital, Milan, Italy. Forty-five singleton pregnancies with a diagnosis of gestational diabetes but free of any other maternal disease known to affect fetal growth, such as autoimmune diseases, chronic hypertension or pregnancy-induced hypertension, and endocrine diseases, were included in the study. The diagnosis of gestational diabetes was made according to the following diagnostic protocol approved by the Ethical University Committee. A 1-hour oral glucose-screening test (140 mg/dL) was usually performed at 24-28 weeks of gestation in all pregnant women without either anamnestic or present risk factors for gestational diabetes. Patients with a previous abnormal 1-hour oral glucose challenge test (140 mg/dL) underwent a 3-hour oral glucose tolerance test (OGTT) after 3 days of free diet containing at least 150 g of carbohydrates per day. The OGTT was performed in quiet maternal conditions, without the use of nicotine or caffeine. Diabetes was diagnosed in the presence of at least two abnormal glycemic determinations during the OGTT (17). After diagnosis, all patients underwent 7- to 10-day diet to normalize caloric and nutritive maternal intake. The daily caloric intake was calculated according to the ideal maternal weight and gestational age. Self-monitoring of blood glucose started immediately and each patient underwent serial pre- and post-prandial glycemia determinations, with a glycemic target <90 mg/dL during fasting and <120 mg/dL two hours postprandially. Patients with normal glucose concentrations underwent a diet only treatment, whereas in the abnormal daily glycemia detection group, a combined diet and insulin treatment was required.

The maternal pregestational Body Mass Index (BMI) was calculated as follows: BMI=pre-gestational maternal weight (kg)/height^2 (m^2).

Gestational age was first calculated according to the last menstrual period and confirmed by ultrasound fetal biometry performed at 20-22 weeks of gestation. All pregnancies were singleton and neither ultrasound detectable fetal anomalies nor chromosomal abnormalities were detected.

Each patient underwent a 2-dimensional sonographic evaluation of both lean and fat fetal body mass at the time of diagnosis. Fetal lean body mass was estimated by means of the traditional fetal auxologic parameters (biparietal diameter, head and abdominal circumference, femur length). The thickness of the subcutaneous fat tissue of the anterior abdominal wall was used to estimate the fetal fat body mass. A transversal section of fetal trunk at the level of abdominal circumference was obtained with fetal abdomen free from contact with arms or legs and with amniotic fluid between the fetal trunk and the uterine wall. Once this section was acquired, a magnification of anterior abdominal wall was obtained. Subcutaneous fetal fat tissue was recognized as an external hyperechogenic surface. The thickness of this layer was measured by placing one caliper exactly between the amniotic fluid and fetal skin and the other caliper exactly between the subcutaneous fat layer and the anterior side of the liver in contact with the anterior abdominal wall. Ultrasound examination was performed every 4 weeks.

Perinatal outcomes, such as gestational age at delivery and neonatal and placental weights were considered.

All maternal and fetal findings in the study population were compared with a series of pregnancies at low-risk of gestational diabetes. We recruited 25 non-smoking women with singleton pregnancies, normal pre-gestational BMI (ranging from 18 to 25), and normal 1-hour glucose screening test performed between 24th and 28th week of gestation, who were free of medical or obstetric disorders known to affect fetal growth. They underwent sonographic evaluation of fetal biometry and subcutaneous fetal tissue thickness at the recruitment time (19-25 weeks of gestation) and every 4 weeks until delivery.

Comparisons between groups were performed by unpaired Student's t-test.

Results

Sixteen out of the 45 pregnancies with gestational diabetes were included in the diet only treatment group, whereas 29 patients were in combined diet and insulin treatment group. A statistically significant difference was observed for maternal age, gestational age at recruitment, and pre-gestational BMI between combined diet and insulin treatment group and group of pregnant women with normal 1-hour glucose challenge test. The comparison between diet only treatment group and normal 1-hour glucose challenge test series showed a significant difference only for gestational age at recruitment (Table 1). Perinatal outcomes in combined diet and insulin treatment group and normal 1-hour glucose challenge test group did not differ, whereas the comparison between neonatal data of gestational diabetes group on diet treatment and normal 1-hour glucose challenge test group showed a statistically significant difference in terms of neonatal weight at birth, and a slight but not significant increase in placental weight (Table 2).

Figure 1 presents fetal abdominal circumference in the two gestational diabetes groups and in normal 1-hour glucose challenge test pregnancies

Table 1. Maternal characteristic: comparison between gestational diabetes (GD) groups and normal 1-hour glucose challenge test group

Maternal characteristics (median, range)	Normal	GD treatment group				
		dietetic	p[a]	dietetic-insulin	p[a]	
No.	25	16		29		
Age (years)	30 (24–36)	31 (29–33)	ns	32	(26–41)	0.05
Gestational age at recruitment (weeks)	22 (19–25)	32 (26–33)	<0.001	30	(24–37)	<0.001
Pre-gestational BMI[b]	21.3 (18–25)	23.1 (16–32)	ns	25.0	(19–40)	0.01

[a]Statistical significance of difference was tested between each GD group and normal 1-hour glucose challenge test group; ns – not significant.
[b]Body mass index.

plotted on the normal percentiles derived from the local normal population (18). No significant differences were found between the two gestational diabetes groups and normal data, although after 30 weeks of gestation, abdominal circumferences in the whole group on diet only treatment and 80% in the group on combined diet and insulin treatment were above the 50th percentile. A significant difference in the thickness of subcutaneous fetal fat tissue between gestational diabetes groups and normal 1-hour glucose challenge test group was found at the time of gestational diabetes mothers recruitment (between 24 and 32 weeks), whereas no significant differences were observed after an adequate treatment (32-36 weeks and 36-40 weeks)(Fig. 2).

Discussion

We evaluated the features of intrauterine growth by a prenatal indirect estimation of ultrasound biometric parameters and by data obtained at birth in pregnancies complicated by gestational diabetes. Both an excessive fetal growth and a high fat tissue thickness can be prenatally evidenced by an ultrasonographic approach. A recent randomized study (14) suggested that the measurement of abdominal circumference is more effective than maternal glucose serum concentrations in determining the need of a combined diet and insulin treatment in patients with gestational diabetes. The simple optimal metabolic control in the mother does not seem to be sufficient to avoid macrosomia in the fetus.

The abdominal circumference is the more sensitive biometric parameter for the presence of factors able to enhance or compromise fetal growth process. In fact, intrauterine growth restriction is early characterized by a remarkably reduced abdominal biometry.

We also considered maternal factors able to affect *in utero* growth process, such as maternal age and pre-gestational BMI. In our study, pre-gestational BMI was significantly higher in combined diet and insulin treatment group than in normal 1-hour glucose screening patients. These data suggest that maternal obesity represents both a risk factor for gestational diabetes and a factor predicting the need for insulin to obtain euglycemia after diagnosing pregnancy-induced diabetes. This is probably due to a higher peripheral insulin-resistance condition.

No preterm deliveries occurred in this study; gestational age at delivery ranged from 36 to 41 weeks, both in the two gestational diabetes groups and in control series with no gestational diabetes. This result could probably be due to the recruitment selection. All the included patients underwent a gestational diabetes screening in the second gestational trimester. This clinical management certainly excluded the pregnancies in which gestational diabetes remained undiagnosed for several weeks, increasing the risk of preterm delivery and perinatal morbidity.

No significant difference in neonatal weights was observed between combined therapy group and normal cases, whereas a statistically significant difference was found between diet only treatment group and normal cases. These findings are in agreement with a previous study by Mello et al

Table 2. Neonatal outcomes: comparison between gestational diabetes (GD) groups and normal 1-hour glucose challenge test group

Neonatal characteristics (median, range)	Normal	GD treatment group				
		dietetic	p[a]	dietetic-insulin	p[a]	
No.	25	16		29		
Gestational age at delivery (weeks)	39 (36–41)	39 (36–41)	ns	39	(36–41)	ns
Neonatal weight (g)	3,228 (2,440–3,970)	3,858 (2,620–4,810)	0.04	3,330	(2,550–4,490)	ns
Placental weight (g)	508 (420–580)	643 (500–940)	ns	581	(500–800)	ns

[a]Statistical significance of differences was tested between each GD group and normal 1-hour glucose challenge test group; ns – not significant.

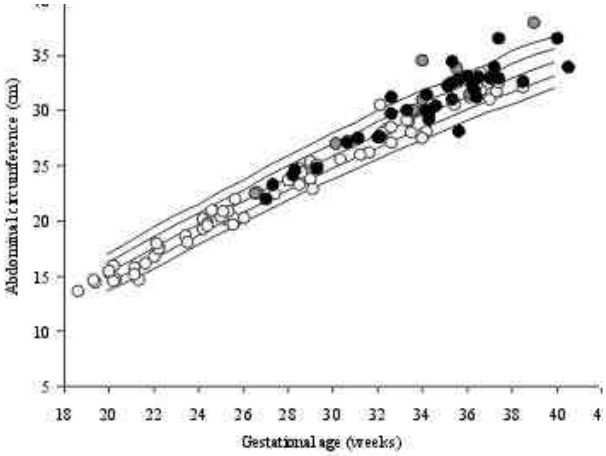

Figure 1. Relationship between abdominal circumference and gestational age in fetuses of gestational diabetic mothers and in normal fetuses plotted on normal reference ranges. Open circles – normal 1-hour glucose challenge test group; gray circles – dietetic treatment group; closed circles – combined dietetic and insulin treatment group; continuous lines – normal ranges of fetal abdominal circumference (10th, 25th, 50th, 75th, and 90th percentiles).

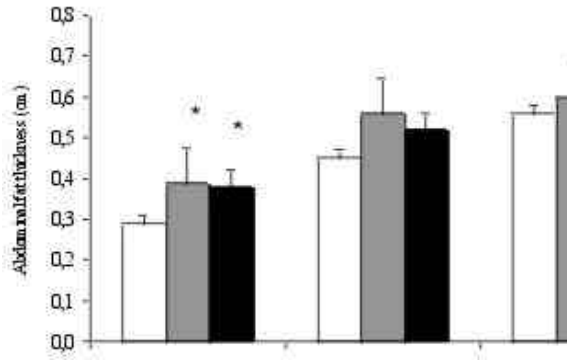

Figure 2. Fetal abdominal fat thickness at different gestational age intervals in gestational diabetes treatment groups compared to normal fetuses. Open columns – normal 1-hour glucose challenge test group; gray columns – dietetic treatment group; closed columns – combined dietetic and insulin treatment group. Asterisks indicate a statistically significant difference of dietetic treatment group ($p=0.044$) and combined dietetic and insulin treatment group ($p=0.048$) versus normal 1-hour glucose challenge test group.

(19), suggesting that the treatment with both diet and insulin is able to normalize fetal growth better then diet only. Moreover, 3 out of 45 diabetic fetuses (6.7%) developed macrosomia: this incidence is higher than in normal pregnancies, but making any consequent statistic conclusions is limited by the small number of patients.

The longitudinal sonographic evaluation of fetal fat abdominal wall thickness showed a reduction of subcutaneous fat growth rate along the gestation in gestational diabetes. In fact, a significant difference between the study group and the normal cases was detected at the time of the diagnosis but these differences were not evident after the onset of the adequate treatment. We speculate that maternal therapy of gestational diabetes could influence fetal growth process, reducing the prevalence of macrosomia at birth.

Furthermore, the observed increase in fetal fat tissue thickness in gestational diabetes could be used as a new criterion to directly estimate fetal metabolic and endocrine status besides the traditional indirect evaluation based on maternal glucose serum determinations. Further clinical studies are needed to confirm these preliminary data.

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