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Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus

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***Objective*:** To determine the contribution of maternal glucose and lipids to intrauterine metabolic environment and fetal growth in pregnancies with gestational diabetes(GDM).

Research design and methods: In 150 pregnancies, serum triglycerides, cholesterol, free fatty acids(FFA), glycerol, insulin and glucose were determined in maternal serum during 3rd trimester and cord blood. Maternal glucose values came from the oGTT and glucose profiles. Measurements of the fetal abdominal circumference(AC) were performed simultaneously with maternal blood sampling and birth weight, BMI and neonatal fat mass were obtained following delivery.

***Results*:** Maternal TG and FFA correlated with fetal AC size (at 28 weeks: triglycerides:p=0.001; FFA:p=0.02) and at delivery with all neonatal anthropometric measures (for FFA: birth weight, p=0.002; BMI, p=0.001; fat mass, p=0.01). After adjustment for confounding variables maternal FFA and triglycerides at delivery remained as the only parameters independently related to LGA (p=0.008, p=0.04). Maternal FFA levels were higher in those with LGA than AGA newborns (362.8$\pm$101.7 vs 252.4$\pm$10.1, p= 0.002). Maternal levels of triglycerides, FFA, and glycerol at delivery correlated with those in cord blood. (p=0.003;p=0.004;p=0.005). Fetal triglycerides and cholesterol levels were negatively correlated with newborn birth weight (p=0.001), BMI (p=0.004;) and fat mass (p=0.001). TG were significantly higher in SGA compared to AGA or LGA newborns while insulin/glucose ratio and FFA were the highest in LGA.

***Conclusion*:** In well controlled GDM pregnancies, maternal lipids are strong predictors for fetal lipids and fetal growth. Infants with abnormal growth seem to be exposed to a distinct intrauterine environment compared to those with appropriate growth.

There is strong evidential support for the "fetal origins" hypothesis which connects adulthood hypertension, insulin resistance and dyslipidaemia to adverse intrauterine conditions during gestation that might be associated with disproportionate fetal growth. An increased risk for adult metabolic disorders is well documented for subjects born growth retarded (1). In addition there is substantial data indicating that accelerated fetal growth predisposes to later obesity (2), especially in diabetic pregnancies. (3). Therefore, normalization of fetal growth is a principle in the management of pregnancies with diabetes. Therapeutic strategies that focus on tight glucose control have often limited success in avoiding accelerated growth, and may even result in growth restriction. In overweight pregnant women, fetal growth seem to be determined only to a small extent by maternal glucose values (4) and normalization of fetal growth may only be achieved by the addition of insulin therapy despite apparently good glucose control with diet. (5)

In view of increasing evidence that obesity, diabetes and cardiovascular diseases in later life may have prenatal antecedents, investigation of the determinants of intrauterine environment and fetal growth have become an important area of research. Variation of birth weight is strongly determined by neonatal fat mass and it is likely that fetal growth disorders might also result from variations in maternal and fetal lipid metabolism. In non-diabetic pregnancies maternal triglycerides have been shown to be correlated with birth weight. (6-9)

Our study aimed to determine the potential relationship of maternal serum glucose and lipids to intrauterine metabolic environment and fetal growth during late pregnancy in well controlled gestational diabetic women. Therefore we investigated the correlation of maternal serum lipid and glucose parameters, measured at different time points in the third trimester of pregnancy, with fetal and neonatal anthropometric parameters and with the correspondent parameters in cord blood representing the current intrauterine metabolic environment of small-, appropriate- and large-for-gestational-age (SGA, AGA and LGA) newborns from pregnancies complicated by gestational diabetes (GDM).

RESEARCH DESIGN AND METHODS

The study population was derived from a prior intervention study that compared different management strategies in GDM. (10) All women had GDM diagnosed based on a 75g oGTT with determination of 3 glucose values in capillary blood using the hexokinase method; at least two values had to exceed the Carpenter & Coustan criteria which are endorsed by the ADA (95180/155 mg/dl) for measurements in venous plasma. With respect to lower glucose concentrations in capillary compared with venous blood, the threshold for fasting glucose was modified into 90 mg/dl while post challenge capillary glucose levels correspondent with those in venous blood. (11) The women were given dietary instruction and performed blood glucose selfmonitoring. Additional insulin therapy was given either based principally on maternal glucose levels or on fetal growth as described previously. (10) Data regarding maternal and neonatal characteristics and maternal glucose values from the diagnostic oGTT and mean fasting and postprandial values from glucose profiles measured twice weekly were extracted from the database of the primary study.

Maternal blood samples were scheduled to be taken at entry to the study (about 28 weeks of gestation), at 32, 36 and 39 weeks. Serum samples were frozen and stored at -80 °C until analysis. Cord blood samples were taken

immediately following delivery and serum was stored at -80°C. Insulin was determined by ELISA (Pharmacia, Uppsala, Sweden); triglycerides , free fatty acids (FFA) and cholesterol were measured by commercial kits (Menarini Diagnostic, Florence, Italy, for triglyceride and cholesterol and Wako Chemical GmbH, Neuss, Germany, for FFA). Glycerol was determined using a fluorometric method.

Fetal growth was measured by ultrasound performed at the same time as the maternal blood sampling. For analysis we focused on the abdominal circumference (AC) since the growth differences of the AC is mainly determined by the thickness of insulin sensitive subcutaneous fat. Birth weight and length was obtained shortly after delivery, and neonatal skinfolds thickness at the flank was measured within 48 hours. Neonatal fat mass was calculated by a formula derived from Catalano et al. (12) that includes birth weight and length and flank skinfolds measurement: 0.30055 (birth weight) + 0.0453 (flank skinfold) – 0.03237 (length) + 0.54657. The correlation with the fat mass values obtained by total body electric conductivity which is considered as gold standard was reported to be very high (R^2=0.78, p=0.001).(12) Infants with birth weight < 10^{th} percentile were classified as SGA, and those with birth weight > 90^{th} percentile as LGA based on gestational age and sex adjusted birth weight percentiles derived from a German national database. (13)

Data management and analysis was performed using SPSS 12.0 (Chicago, IL). Results are expressed as means $\pm$ SD. Relationship between variables were analyzed by bivariate correlation applying the Spearman test. Differences between groups were analyzed by using ANOVA test with Bonferroni adjustment. Multiple logistic regression analysis was performed to determine maternal parameters independently associated with birth weight . All statistical tests were two-tailed and a p value of < 0.05 was considered significant.

RESULTS

From the original study population (10), 150 mother-newborn pairs were selected based on the availability of complete samples of maternal blood and of cord blood. Maternal and neonatal characteristics are detailed in table 1, metabolic parameters measured in maternal blood taken close to delivery (between 36 and 39 weeks of gestation, in most cases one week to delivery) and in cord blood are shown in table 2. The remaining women from the primary study who could not be included in the presented study due to missing cord blood samples were not significantly different from the included cases regarding maternal or newborn characteristics.

Except for glucose, the concentration of all parameters determined in the mother`s serum were significantly higher than in the correspondent cord blood serum. When all the individual paired samples were compared, only maternal levels of triglcerides, FFA (figure 1), and glycerol close to delivery correlated significantly with those in cord blood (r=0.19, p=0.003; r=0.28, p=0.004; r=0.26,p=0.005, respectively).The relationship between the different maternal metabolic parameters during third trimester and fetal growth was evaluated by their correlation with the fetal AC measured at entry to the study (28.3 $\pm$ 2.4 weeks of gestation) and at 32 and 36 weeks. Both maternal triglycerides and FFA correlated positively and significantly at each of the studied time points with fetal AC size (for entry: triglycerides r=0.26, p=0.001, FFA see fig 1). However, there were no significant correlations between fetal growth and any maternal glucose values either from the oGTT or from the selfmonitoring glucose profiles performed at entry, and at 32 and 36 weeks (data not shown). Maternal parameters from

blood samples taken close to delivery were compared with neonatal anthropometric measures. Maternal plasma FFA and glycerol levels were significantly related to all anthropometric measures of newborns (for glycerol vs. birth weight r=0.23, p=0.3, BMI r=0.24, p=0.006 or fat mass r=0.23, p=0.01; for FFA vs. birth weight r=0.27, p=0.002, BMI r=0.3,p=0.001 or fat mass, displayed in figure 1). Maternal triglycerides had a positive correlation with newborn fat mass (r=0.17, p=0.03) but not with birth weight or neonatal BMI. After adjustment for maternal prepregnancy BMI, weight gain, age, parity, fasting and postprandial glucose from the profiles at 36 weeks and close to delivery only maternal FFA and triglycerides remained independently related to LGA (adjusted p=0.008 and p= 0.04, respectively). Maternal FFA levels were significantly higher in mothers with LGA infants compared to mothers with AGA newborns (362.8 $\pm$ 101.7 uM vs 252.4 $\pm$ 10.1 uM, p= 0.002).

On the neonate´s side, cord triglycerides and cholesterol levels correlated negatively and significantly with both birth weight (figure 2), BMI (r=-0.24,p=0.004;) and fat mass (figure 2), whereas insulin and the insulin/glucose ratio correlated positively and significantly with birth weight (r=0.23,p=0.006; r=0,19, p=0.03), BMI (r=0,24 ,p=0.005; r=0.21, p=0.12) and fat mass (r=0.21,p=0.02; 0.17, p=0.48) . None of cord blood glucose, glycerol or FFA showed any significant correlation with the neonatal size. Cord blood triglycerides levels of SGA newborns were significantly increased compared to AGA or LGA newborns (table 2), while insulin, insulin/glucose ratio and FFA were the highest in LGA infants.

DISCUSSION

The present findings demonstrate that circulating maternal lipids but not glucose values correlated with fetal growth at different time points during the third trimester in a population of well controlled GDM pregnancies. Besides, maternal FFA und triglyceride levels close to delivery predicted LGA birth weight independently of maternal BMI and both maternal FFA, triglyceride and glycerol concentrations correlated to those measured in fetal serum. Fetal blood of SGA newborns showed high triglyceride levels while LGA newborns were characterised by high FFA concentration, a high insulin/glucose ratio and low TG levels

Both, maternal triglyceride and FFA levels correlated with fetal growth during pregnancy and with neonatal anthropometric measures, the best correlation being found with neonatal fat mass. Maternal hypertriglyceridemia is a characteristic feature of pregnancy (14) and although maternal circulating triglyceride do not directly cross the placenta (15) the presence of lipoprotein receptors, fatty acid-binding proteins (16) and different lipase activities in the placenta, allows the efficient transfer of maternal fatty acids to the fetus. It had been previously shown that the concentration of triglycerides in third trimester is a stronger predictor of birth weight than glucose parameters (6-8). Published data have been limited to a one time-point measurement in conjunction with the oGTT whereas this study considers lipid and glucose data at different times during the 3rd trimester and close to delivery (approximately one week to delivery). Due to the strict primary protocol of the investigated study cohort, our study population presented a tight and stable glucose control which may have attenuated the impact of variations in maternal glycemia on fetal growth. But even at study entry glucose values were not related to fetal growth and from clinical experience we know that good glucose control does not necessarily prevents accelerated growth especially in obese women. The success of additional insulin therapy to lower the macrosomia rate in obese women with normal glucose values as demonstrated by Langer et

al. (5) may be in part the result of the anti-lipolytic effect of insulin. This action would decrease maternal FFA and triglyceride levels, reducing their potential effect on fetal fat mass. This may explain the normalization of macrosomia rates observed in studies that applied a fetal-growth-based approach of individualized GDM therapy. Insulin therapy was given to women with accelerated fetal growth as indicated by the fetal AC>75th percentile despite maternal glucose being maintained within the target range. (10,18) Our findings are in accordance with Kitijama and Knopp who showed that high maternal triglyceride levels predicted macrosomia and this was independent of maternal BMI. (6,7)

The potential importance of maternal lipids for the development of the fetus was underlined by the fact that both cord blood FFA and triglyceride levels seemed to be tightly associated with maternal lipids. There is a paucity of studies published so far comparing maternal and fetal lipid parameters. In contrast to our data obtained in a well controlled GDM population, Merzouk reported that maternal triglyceride levels in late gestation had been a significant predictor of elevated fetal lipids only in a group of poorly controlled diabetic mothers but not in well controlled type 1 diabetics. (19) In another study the same authors reported correspondent lipoprotein abnormalities (elevated triglyceride, cholesterol, Apo B 100) only in obese mothers and their macrosomic infant. (20)

The most striking finding from this study was that fetal triglycerides were negatively correlated to birth weight resulting in significantly higher triglyceride levels in SGA newborns compared to AGA or LGA born infants. There are previous studies demonstrating elevated triglyceride levels in cord blood of growth retarded newborns (21,22). A theoretical explanation for the inverse correlation between fetal triglycerides and birth weight might be reduced lipoprotein lipase (LPL) activity. LPL present in the capillary endothelium of extrahepatic tissues catalyses the hydrolysis of triglyceride -rich lipoproteins (namely chylomicrons and VLDL) and their products, FFA and glycerol are taken up by the adjacent tissue. Since it is known that the expression of LPL is strongly associated with the development of adipose tissue, we hypothesize that SGA newborns might have a low LPL activity which would be responsible for their augmented circulating triglyceride levels. By contrast low triglyceride levels found in LGA newborns would be the result of enhanced LPL activity derived from their increased adipose mass. Interestingly, in the pediatric literature there are also reports of high triglyceride levels in the serum of SGA newborns taken a few days after delivery (23,24), especially in infants with a Ponderal index < 10th (24). This fits with our observations and suggests that SGA infants appear to have impaired utilization of circulating triglycerides, as a consequence of lacking peripheral adipose.

In relation to the question of whether infants with abnormalities in growth are exposed to a different intrauterine environment compared to those with appropriate growth, our data demonstrated that both newborns with impaired or accelerated growth show metabolic abnormalities but of different character. SGA newborns had been exposed to high levels of triglycerides while LGA infants showed already intrauterine signs of insulin resistance indicated by the high insulin/glucose ratio. This could be responsible for the elevated FFA levels found in the LGA infants, which might reflect a reduced effect of insulin inhibiting lipolysis or augmented lipolytic activity due to their increased adipose tissue mass. How these metabolic patterns contribute to the known disposition of SGA and LGA newborns for obesity, diabetes and cardiovascular disorders in later life remains to be further illuminated. From animal models

we know that induced hyperinsulinism in the area of the hypothalamus region during the perinatal phase leads to later obesity. Little is known about the long-term effects of intrauterine hypertriglyceridemia. We do know that blood lipoprotein abnormalities in childhood are predictive for those in adulthood (25) and it is likely that this is also true during very early life which is a very sensitive time.

In summary, these findings show the effect of a disturbed maternal lipid metabolism on the fetal metabolic environmental and fetal growth that may have long-term consequences.

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Table 1: Maternal and offspring characteristics of pregnancies with GDM

MOTHER		**OFFSPRING**	
Maternal characteristics		**Neonatal characteristics**	
Age (years)	31.2 ± 4.9	Gestational age at delivery (weeks)	39.2 ± 1.4
Parity	2.05 ± 1.2	Birth weight (g)	3389.81 ± 503
Prepregnancy BMI (kg/m^2)	27.8 ± 6.2	BMI (kg/m^2))	13.0 ± 1.3
Gestational age at diagnosis (weeks)	25.9 ± 4.4	Fat mass (g)	432.1 ± 162.6
oGTT fasting (mg/dl)	94.3 ± 13.9	LGA (%)	13.1
1 hr	202.3 ± 26.9	SGA (%)	12.9
2 hr	158.3 ± 31.8	C-section rate (%)	11.7
Gestational age at entry (weeks)	28.3 ± 2.4		
Glucose profiles at entry (mg/dl) mean fasting glucose	87.9 ± 10.9		
mean postprandial glucose	113.5 ± 15.3		
Glucose profiles close to delivery (mg/dl) mean fasting glucose	83.5 ± 10.7		
mean postprandial glucose	109.2 ± 13.7		

Table 2. Metabolic parameters in maternal serum close to delivery and in cord blood of all the offspring and in categories of SGA, AGA and LGA newborns from mothers with GDM (mean ± SD)

	MOTHER	**OFFSPRING**			
		Total N=150	**SGA** N=20	**AGA** N=111	**LGA** N=19
Glucose (mg/dl)	84.2 ± 18.3	85.0 ± 21.4	82.6 ± 28.6[a]	86.0 ± 21.0[a]	80.3 ± 13.7[a]
Insulin (uU/ml	25.2 ± 21.7*	10.2 ± 6.25	8.1 ± 10.0[a]	8.6 ± 5.3[a]	20.8 ± 6.9[b]
Ins/Glucose	0.29 ± 0.21**	0.07 ± 0.002	0.06 ± 0.01[a]	0.03 ± 0.005[a]	0.26 ± 0.08[b]
Triglycerides (mg/dl)	265.9 ± 87.6**	41.6 ± 21.8	62.1 ± 27.5[a]	40.3 ± 22.6[b]	32.0 ± 17.5[b]
Cholesterol (mg/dl)	253.7 ± 55.6**	63.5 ± 17.7	64.5 ± 14.4[a]	63.3 ± 18.7[a]	63.5 ± 12.4[a]
Glycerol (µM)	202.4 ± 100.3**	76.1 ± 64.2	107.4 ± 123[a]	70.5 ± 54.0[a]	101.5 ± 83.2[a]
FFA (µM)	262.5 ± 112.4**	146.3 ± 88.2	189.0 ± 78.0[a,b]	135.2 ± 75.8[a]	213.0 ± 149.8[b]

Difference between maternal serum and cord blood (Total offspring):
*$p < 0.05$, ** $p < 0.001$
Difference between SGA, AGA and LGA newborns:
Different superscript letters indicate $p < 0.05$

Legends

Figure 1

Correlation of maternal serum FFA with fetal growth and fetal FFA.

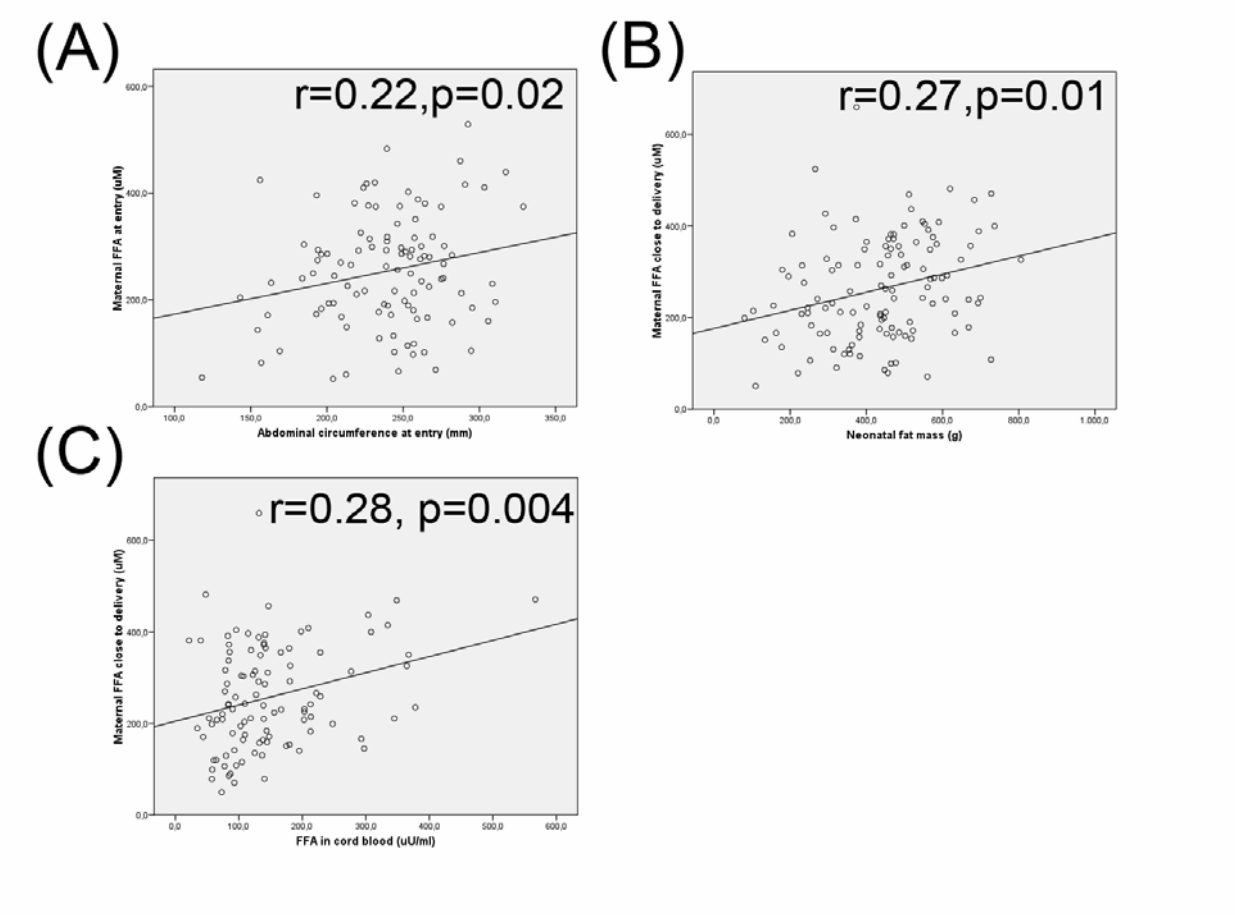
(A) maternal FFA at entry to the study with about 28 weeks of gestation with fetal abdominal circumference at entry,

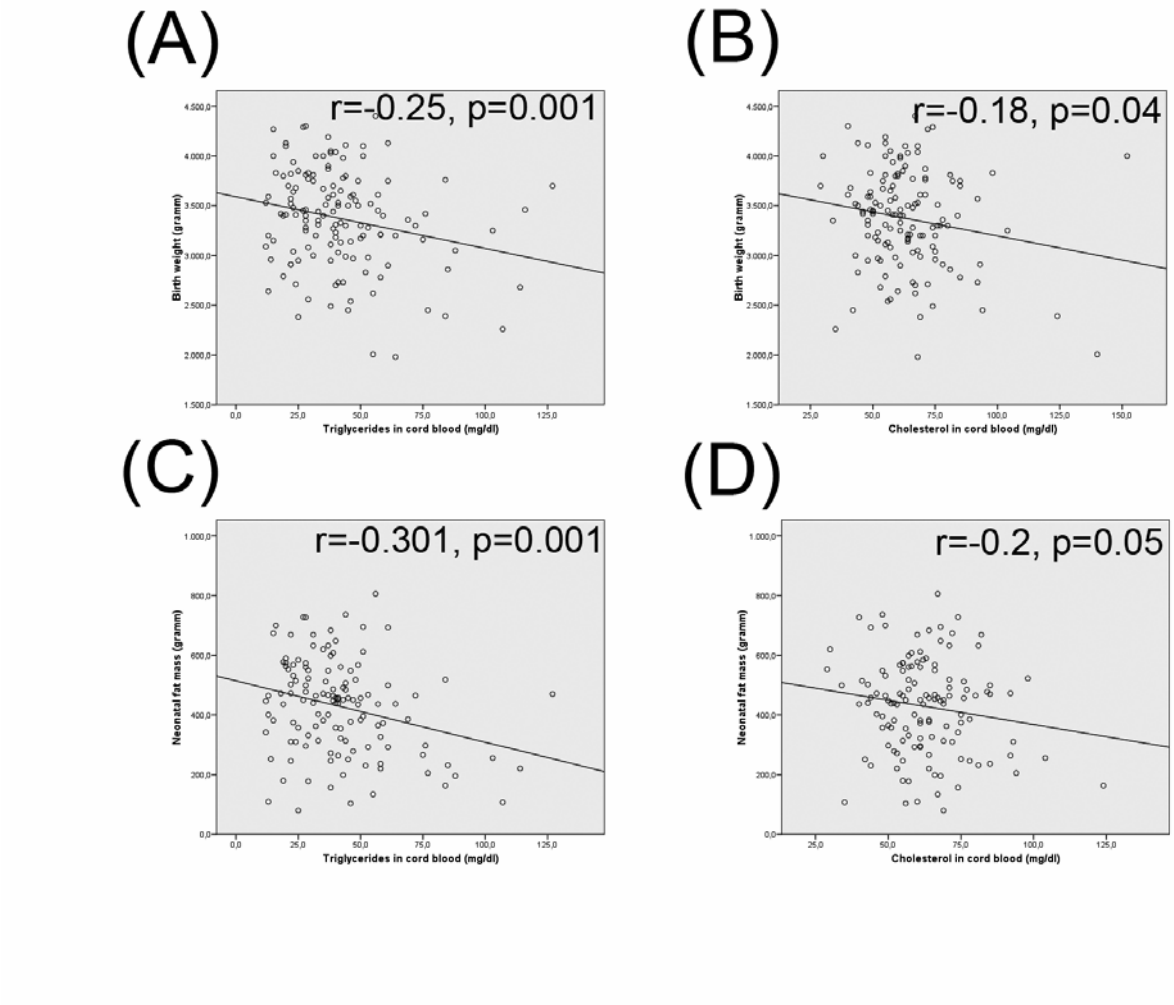
(B) maternal FFA close to delivery with neonatal fat mass

(C) maternal FFA close to delivery with fetal FFA measured in cord blood serum

Figure 2

Correlation of cord blood serum triglycerides and cholesterol with birth weight and neonatal fat mass




(A)
r=-0.25, p=0.001
Birth weight (gramm)
Triglycerides in cord blood (mg/dl)
(B)
r=-0.18, p=0.04
Birth weight (gramm)
Cholesterol in cord blood (mg/dl)
(C)
r=-0.301, p=0.001
Neonatal fat mass (gramm)
Triglycerides in cord blood (mg/dl)
(D)
r=-0.2, p=0.05
Neonatal fat mass (gramm)
Cholesterol in cord blood (mg/dl)