# Gestational Diabetes Mellitus Causes Changes in the Concentrations of Adipocyte Fatty Acid–Binding Protein and Other Adipocytokines in Cord Blood

Henar Ortega-Senovilla, phd[1]
Ute Schaefer-Graf, md[2]
Katrin Meitzner, md[2]
Michael Abou-Dakn, md[2]
Kristof Graf, md[3,4]
Ulrich Kintscher, md[5]
Emilio Herrera, phd[1]

**OBJECTIVE**—To determine the concentrations of adipocyte fatty acid–binding protein (AFABP) and other adipocytokines in maternal and cord serum of pregnant women with gestational diabetes mellitus (GDM) and of control subjects and to relate them to indexes of insulin sensitivity.

**RESEARCH DESIGN AND METHODS**—In 86 control and 98 GDM pregnant women, venous blood was collected before vaginal delivery and arterial blood from cord immediately after delivery. Serum insulin and adipocytokines were measured by enzyme-linked immunosorbent assay (ELISA).

**RESULTS**—GDM women had higher prepregnancy BMI, and data were adjusted for it. Maternal serum insulin, insulin-to-glucose ratio, homeostasis model assessment (HOMA), AFABP, and retinol-binding protein 4 (RBP4) were higher and adiponectin was lower in GDM than in control subjects, whereas serum glucose, insulin, insulin-to-glucose ratio, HOMA, nonesterified fatty acids, and RBP4 were higher and glycerol, AFABP, and adiponectin were lower in cord blood serum of GDM than of control subjects. AFABP and adiponectin in cord serum of control subjects were higher than in maternal serum; in GDM women no difference was found for AFABP in cord versus maternal serum, although adiponectin remained higher in cord. Values of leptin in both groups were lower in cord than in maternal serum, and those of RBP4 were lower in only GDM women.

**CONCLUSIONS**—It is suggested that fetal tissues are the main source of cord arterial serum AFABP, and in GDM fetuses AFABP values correlate with adiposity markers. A downregulation of adiponectin and upregulation of RBP4 in GDM mothers and their fetuses may be related to their insulin-resistant condition, whereas changes in AFABP do not seem to be related.

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Pregnancy is associated with substantial changes in maternal metabolism, which provide sufficient energy and nutrients to the fetus. Glucose is the primary source of energy for the fetoplacental tissues but, because the fetus only produces glucose under extreme conditions, it is necessary to ensure its transport through the placenta. In this context, the mother develops a state of insulin resistance during midpregnancy and progressing through the third trimester, which reduces the consumption of glucose by maternal tissues and increases gluconeogenesis enabling a sufficient supply of glucose to the fetus (1). This causes a positive maternal-fetal glucose gradient, which facilitates its placental transfer. However, in a substantial proportion of pregnancies, the insulin-resistant condition is greatly increased and gestational diabetes mellitus (GDM) develops (2); the consequent adverse metabolic state results in complications for the mother, the fetus, and the neonate (3).

The mechanisms responsible for the development of GDM are unclear, but mechanisms similar to those in type 2 diabetes have been implicated (4), supporting the notion that the two conditions have similar underlying pathophysiology. Adipose tissue secretes several specific proteins called adipocytokines that modulate the action of insulin in different tissues (5), suggesting that alterations in the expression and secretion of these factors may be linked to GDM and related diseases. Recently, adipocyte fatty acid–binding protein (AFABP), a member of the mammalian intracellular fatty acid–binding protein multigene family (6), was described as a novel adipocytokine. This protein is responsible for intracellular fatty acid trafficking and contributes to the regulation of hormone-sensitive lipase activity (7). Moreover, mice deficient in AFABP are protected from development of hyperinsulinemia, hyperglycemia, and insulin resistance (8,9). Recent studies have shown that AFABP is present in human serum (10), and its levels are associated with insulin resistance and type 2 diabetes (10,11). Therefore, in adults, AFABP concentrations have been considered an independent predictor of diabetes, contributing to the control of systemic insulin sensitivity and of lipid and glucose metabolism. So far there is only one study where the level of AFABP in GDM women at midpregnancy has been determined (12), and no information is available on its levels either during late pregnancy or in cord serum. Thus, the objectives of the current study were to measure the concentrations of AFABP in maternal and cord serum of control and GDM pregnant women and to examine its relationship with glycemia and other related variables.

From the [1]Faculties of Pharmacy and Medicine, University CEU San Pablo, Madrid, Spain; the [2]Department of Obstetrics and Gynecology, St. Joseph's Hospital, Center for Diabetes in Pregnancy, Berlin, Germany; the [3]Department of Medicine/Cardiology, German Heart Institute, Berlin, Germany; the [4]Department of Cardiology, Jewish Hospital, Berlin, Germany; and the [5]Institute of Pharmacology, Center for Cardiovascular Research, Charité, Berlin, Germany.
Corresponding author: Emilio Herrera, eherrera@ceu.es.
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## RESEARCH DESIGN AND METHODS

### Study subjects

The study population was derived from a prior study that compared the implications of maternal lipids on fetal metabolism in GDM and control pregnancies (13,14). Diagnosis of GDM was established by a 75-g oral glucose tolerance test (OGTT) at 26 weeks of gestation (22.6–30.6 weeks) after the diagnostic criteria of Carpenter and Coustan, which are endorsed by the American Diabetes Association (95/180/155 mg/dL; 5.2/10/8.6 mmol/L). All pregnancies were singleton pregnancies without identified fetal anomalies. In full-term offspring (gestational age >37 weeks), birth weight and length were obtained shortly after vaginal delivery, and neonatal skin-fold thickness at the flank was measured within 48 h. Neonatal fat mass was calculated by a formula derived from Catalano et al. (15).

The study protocol was approved by the institutional review board. Informed written consent was obtained from the parents.

### Blood samples

Maternal blood samples were taken at the last visit to the obstetric clinic, no longer than 1 week before delivery. Cord blood samples were taken from one of the umbilical arteries from a segment of the cord, immediately after delivery. All blood samples were centrifuged (1,500 *g* at 4°C for 25 min), and aliquots of serum were immediately stored at −80°C until analysis. None of the samples used in the study showed any hemolysis.

### Analytical determinations

Serum glucose (Abbott Diagnostics), cholesterol, triacylglycerols (TAG; Menarini Diagnostics), glycerol, and nonesterified fatty acids (NEFA; Wako Chemicals GmbH, Neuss, Germany) were determined enzymatically using commercial kits.

Serum insulin, leptin, adiponectin, retinol-binding protein 4 (RBP4), and AFABP concentrations were measured using sandwich ELISA kits according to the manufacturers' instructions. Specifically, insulin and leptin were measured (Mercodia AB, Uppsala, Sweden) with intra-assay variations of 3.4 and 2.3%, and interassay variations of 3.6 and 5.2%, respectively, RBP4 (AdipoGen, Seoul, Korea) with intra-assay variation of 3.4% and interassay variation of 7.1%, and adiponectin and AFABP (BioVendor, Modrize, Czech Republic) with intra-assay variations of 3.0 and 6.5% and interassay variation of 5.3 and 2.6%, respectively. In all cases, the variation was determined using control plasma with certified values of each of the analytes measured.

### Statistics

Results are expressed as means ± SE. Statistical difference between groups was determined by ANOVA, after adjustment for possible confounding factors; when differences were statistically significant, multiple comparisons were performed using the Tukey post hoc test. Given their skewed distributions, concentrations of TAG, NEFA, glycerol, insulin, leptin, adiponectin, and AFABP were log-transformed before statistical comparison. Correlations were tested with Pearson's method using the log-transformed data as indicated. To ascertain the independent predictors of maternal insulin resistance using the homeostasis model assessment (HOMA), stepwise multiple regression analysis with backward selection was performed. All statistical analysis was performed using a computer software package (Statgraphics Centurion XV, version 15.2.06; Statistical Graphics Corporation).

## RESULTS

—Characteristics of the population studied are shown in Table 1. Women with GDM were slightly older and had higher prepregnancy BMI than the normal pregnancy control subjects. They had higher concentrations of glucose at all stages of an OGTT performed at midgestation than the control subjects. All neonates were born near term by vaginal delivery and at similar gestational age. We did not find any statistical differences either in birth weight or fat mass between neonates from the two groups, although the placental weight was lower in the GDM group.

In maternal serum obtained close to term, after adjustment for prepregnancy BMI, it was found that serum glucose was similar in control and GDM pregnant women, but both the concentration of

**Table 1—*Characteristics of mothers and their offspring***

| | Mothers/maternal serum | | Offspring/umbilical cord serum | |
|---|---|---|---|---|
| | Control | GDM | Control | GDM |
| *n* | 86 | 98 | 86 | 98 |
| Age (years) | 28.7 ± 0.5 | 30.9 ± 0.5** | | |
| Prepregnancy BMI (kg/m$^2$) | 25.4 ± 0.6 | 27.3 ± 0.5* | | |
| Gestational age at OGTT (weeks) | 26.9 ± 0.4 | 26.4 ± 0.3 | | |
| Glucose fasting OGTT (mg/dL) | 75.7 ± 1.5 | 95.2 ± 1.1*** | | |
| Glucose 1-h post-OGTT (mg/dL) | 132 ± 3 | 204 ± 2*** | | |
| Glucose 2-h post-OGTT (mg/dL) | 103 ± 4 | 156 ± 3*** | | |
| Gestational age (weeks) | | | 39.4 ± 0.1 | 39.5 ± 0.1 |
| Birth weight (g) | | | 3,487 ± 50 | 3,384 ± 44 |
| Fat mass (g) | | | 418 ± 17 | 445 ± 15 |
| SGA (%) | | | 10 | 11 |
| LGA (%) | | | 14 | 9 |
| Placenta weight (g) | | | 643 ± 13 | 584 ± 11*** |
| Female sex (%) | | | 54 | 50 |
| Glucose (mg/dL) | 90.1 ± 2.1 | 83.9 ± 2.6 | 76.3 ± 2.6[a] | 89.0 ± 2.4***[a] |
| Insulin (μU/mL)[(1)] | 17.7 ± 2.1 | 24.4 ± 2.1** | 4.74 ± 0.56[a] | 8.52 ± 0.51***[a] |
| Insulin/glucose (μU/mg)[(1)] | 19.4 ± 2.1 | 29.7 ± 2.3*** | 6.86 ± 0.72[a] | 9.87 ± 0.67***[a] |
| HOMA[(1)] | 4.26 ± 0.59 | 5.64 ± 0.65** | 0.93 ± 0.13[a] | 1.90 ± 0.12***[a] |
| TAG (mg/dL)[(1)] | 254 ± 9 | 259 ± 8 | 38.2 ± 1.8[a] | 39.8 ± 1.6[a] |
| Glycerol (μmol/L)[(1)] | 189 ± 12 | 198 ± 13 | 93.8 ± 6.1[a] | 73.6 ± 5.9**[a] |
| NEFA (μmol/L)[(1)] | 325 ± 21 | 261 ± 22 | 103 ± 7[a] | 145 ± 7***[a] |

Data are means ± SEM. Maternal serum parameters were adjusted by prepregnancy BMI, and cord serum parameters were adjusted by prepregnancy BMI and sex of neonate. SGA, small for gestational age. LGA, large for gestational age. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, significant differences between control and GDM; [a]$P < 0.001$, significant differences between cord serum compared with the respective maternal value; [(1)]log-transformed skewed data were used for statistical comparisons.

insulin and the insulin-to-glucose ratio were higher in GDM group. The HOMA index of insulin resistance also was significantly higher in GDM compared with control subjects. However, neither TAG nor glycerol and NEFAs was statistically different between control and GDM pregnant women. In serum from cord blood, after adjustment by prepregnancy BMI and by the sex of the neonate, the concentrations of glucose and insulin in the GDM group were significantly higher than in the control group. Similarly, the insulin resistance indexes were higher in cord serum of newborns from GDM pregnant women. The concentration of TAG was similar in both groups, but glycerol was lower and NEFAs were higher in cord serum of GDM subjects. In cord serum, all the analyzed parameters and insulin resistance indexes were significantly lower than in maternal serum, except for the cord serum concentrations of glucose in GDM newborns, which were similar to those found in their mothers' serum.

Maternal serum adipocytokine levels show that whereas AFABP levels in serum were slightly, but significantly, higher in GDM than in control women (17.7 ± 0.8 vs. 19.9 ± 1.0 ng/mL, respectively; $P = 0.0493$), leptin levels did not differ between the two groups; adiponectin levels were lower and RBP4 levels were higher in GDM than in control subjects (Fig. 1). In serum from cord blood, AFABP concentration in GDM was lower than those found in control subjects. In the control group only, AFABP levels in cord serum were significantly higher than in their mothers.

The other adipocytokines measured in cord serum showed the same pattern of differences as that observed in maternal serum. Thus, the concentration of adiponectin was higher in the control than the GDM group, leptin did not differ between groups, and RBP4 was higher in GDM

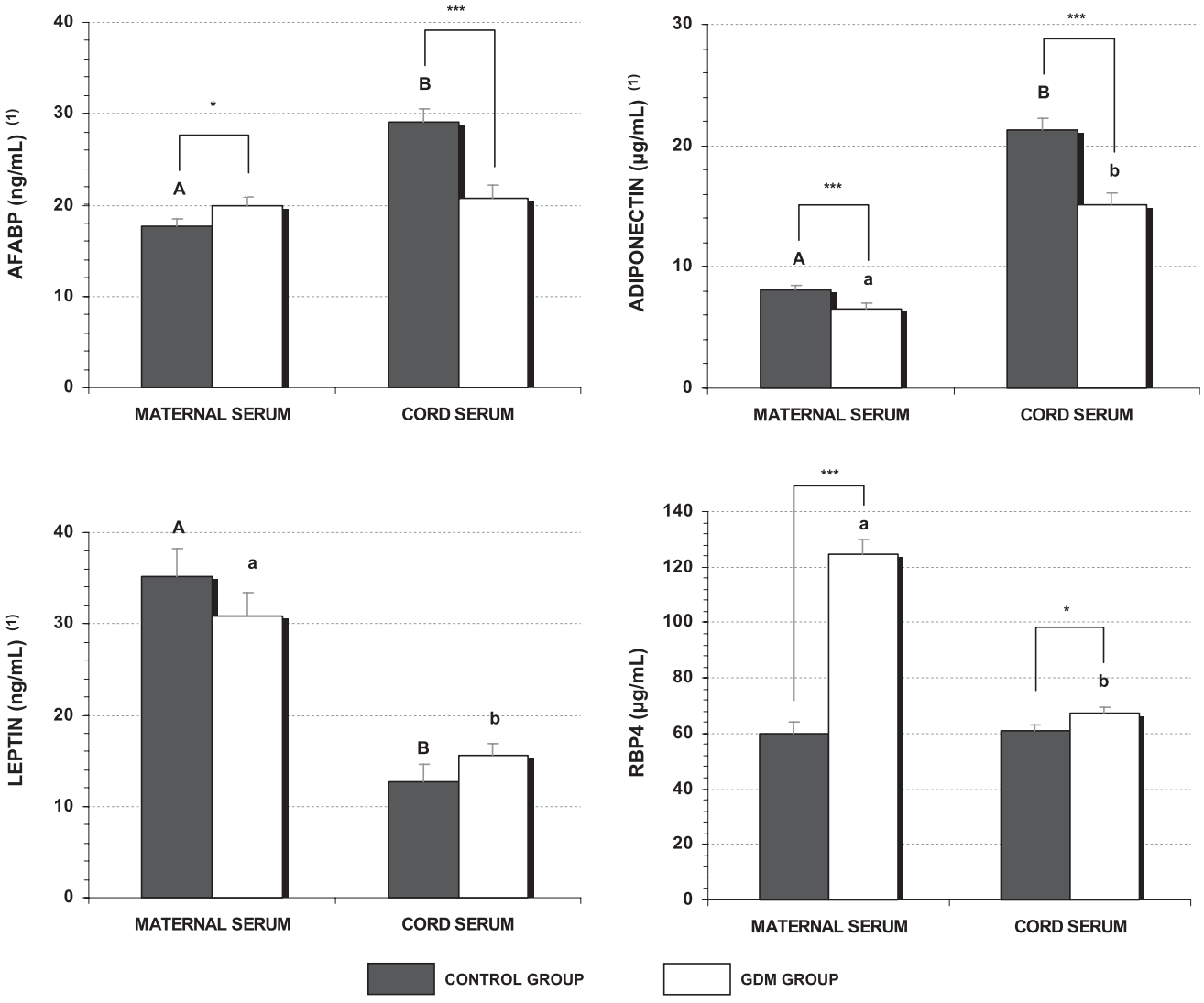


**Figure 1**—*Maternal and cord serum concentrations of AFABP, adiponectin, leptin, and RBP4 in control and GDM pregnant women and their neonates. Maternal and cord serum parameters were adjusted by prepregnancy BMI, and additionally, cord serum parameters were adjusted by the sex of the neonate. Asterisks indicate significant differences between control and GDM groups (*P < 0.05; ***P < 0.001). Different superscripted uppercase letters indicate significant differences between cord and maternal serum in control group (P < 0.001); different superscripted lowercase letters indicate significant differences between cord and maternal serum in GDM group (P < 0.001). Filled bars, data from control subjects; open bars, data from GDM subjects. Data are means ± SEM. (1)Log-transformed for statistical comparisons.*

than control subjects. In both the control and the GDM group, the levels of adiponectin in cord serum were higher than in their mothers unlike leptin, which was lower in cord than in maternal serum. No differences were observed in RBP4 between maternal and cord serum in control subjects, but in GDM subjects, cord levels were significantly lower than those in their mothers.

To test the potential relationship between AFABP levels and the other variables, linear correlations were carried out with individual values in both maternal and cord blood sites, in each case analyzing GDM and control subjects separately. Table 2 summarizes the significant results. Significant correlations were found between AFABP in maternal blood and either prepregnancy BMI or leptin in both control and GDM mothers, whereas correlation coefficients were significant only in control subjects for TAG and only in GDM subjects for RBP4; no correlation with either neonatal fat mass or cord blood AFABP was found. Values of AFABP in cord blood correlated with neonatal fat mass, glycerol, or leptin, only in GDM subjects, and with either glucose or NEFA, only in control subjects.

Multiple regression analysis of the different measured variables was carried out to test the factors independently associated with maternal HOMA values. It was found (Table 3) that only NEFA in pregnant control women, prepregnancy BMI in GDM pregnant women, and leptin values in both control and GDM cord blood were statistically significant.

**CONCLUSIONS**—The current study describes for the first time the serum AFABP levels in cord serum in control and GDM conditions, and in their mothers at late pregnancy (i.e., close to delivery), showing that values are slightly higher in GDM women than in control subjects, whereas AFABP values in cord blood serum are much higher in control subjects. When comparing AFABP concentrations from maternal serum with those from cord serum, similar values in GDM pregnancies were shown, whereas in control subjects the values in cord serum were higher than in their mothers.

Our cohort of GDM pregnant women and the control subjects had similar glucose levels, but serum insulin, insulin-to-glucose ratio, and HOMA values were higher in the GDM group, clearly showing a more highly insulin-resistant condition. Despite this, only a small difference in AFABP levels was found between the two groups, and we found no relationship between the measured indexes of insulin resistance and the circulating concentrations of AFABP in any of the groups. However, as reported in previous studies in overweight/obese adults (9), or in adults with metabolic syndrome (16), AFABP showed a strong association with maternal prepregnancy BMI in both control and GDM women. We also found that maternal serum AFABP concentration was positively correlated with the concentration of leptin, a known marker of adiposity (17). Our findings agree with those of Kralisch et al. (12) who reported higher AFABP levels in GDM pregnant women than in control subjects. To our knowledge this (12) is the only previous study that is similar, but not identical, to the current study. The first difference is that they collected blood at midgestation (28 to 29 weeks), whereas our study collected samples just 1 week before delivery. Finally, although their GDM women had slightly higher basal plasma glucose levels than the control subjects, they found no difference in either insulin or HOMA values (12), whereas our GDM women were normoglycemic but had higher insulin and HOMA values than control subjects. Our results were adjusted by maternal prepregnancy BMI, whereas Kralisch et al. used fasting insulin values; when we corrected AFABP values by insulin, no difference in AFABP between control and GDM women was detected (17.4 ± 1.4 vs. 18.9 ± 2.0 ng/mL, respectively; $P > 0.05$). Therefore, it is unlikely that circulating AFABP is an independent predictor of insulin resistance in pregnant women.

Measurements of AFABP in cord blood serum are reported here for the first time, so we cannot compare our findings with other studies. We measured AFABP in arterial cord blood serum, which would mainly reflect release by fetal tissues rather than from the placenta. Since cord AFABP in control subjects appeared much higher than in the maternal circulation and maternal AFABP concentrations did not correlate with those in cord blood (either in control or GDM subjects) it is proposed that fetal tissues are the main source of AFAPB in cord serum. Cord blood was obtained just after vaginal delivery, and AFABP levels could be influenced by those conditions, whereas maternal blood was collected few days earlier. However, we also carried out the same determinations in neonates of control and GDM mothers delivered by caesarean section, and similar findings were obtained (H.O.-S., U.S.-G., K.M., E.H., unpublished results). Newborns from GDM mothers showed marked insulin resistance, but contrary to expectations, they had lower serum AFABP levels than control subjects. However, a weak but significant negative correlation was found between AFABP and glucose levels in cord blood serum of control but not GDM subjects. This may indicate a role for AFABP in facilitating glucose utilization in fetuses, which does not operate correctly when gestational diabetes is present.

**Table 2—*Correlations between serum AFABP concentrations and anthropometric and metabolic parameters in maternal and cord serum of control and GDM pregnant women and their newborns***

| | Control | | GDM | |
|---|---|---|---|---|
| | AFABP (ng/mL)[(1)] | | AFABP (ng/mL)[(1)] | |
| | *r* | *P* | *r* | *P* |
| Maternal | | | | |
| Prepregnancy BMI (kg/m$^2$) | 0.4201 | 0.0000 | 0.5133 | 0.0002 |
| Leptin (ng/mL)[(1)] | 0.4907 | 0.0007 | 0.5957 | 0.0002 |
| TAG (mg/dL)[(1)] | 0.2261 | 0.0331 | 0.0541 | 0.7121 |
| RBP4 (μg/mL) | −0.0111 | 0.9260 | 0.2882 | 0.0470 |
| Neonatal fat mass (g) | 0.0057 | 0.9596 | −0.0667 | 0.6489 |
| Cord AFABP (ng/mL)[(1)] | 0.1679 | 0.1647 | 0.1373 | 0.1533 |
| Cord | | | | |
| Neonatal fat mass (g) | −0.0982 | 0.3925 | 0.2795 | 0.0174 |
| Glucose (mg/dL) | −0.2232 | 0.0480 | −0.0050 | 0.9659 |
| Glycerol (μmol/L)[(1)] | 0.1782 | 0.1162 | 0.3387 | 0.0034 |
| NEFA (μmol/L)[(1)] | 0.3043 | 0.0064 | 0.1323 | 0.2678 |
| Leptin (ng/mL)[(1)] | −0.2174 | 0.1721 | 0.2983 | 0.0104 |

[(1)]Log-transformed for statistical comparisons.

**Table 3—*Multiple regression analysis showing factors independently associated with maternal HOMA*[(1)]**

| Independent variable | β | *P* | $R^2$ (%) |
|---|---|---|---|
| Control pregnant women | | | |
| NEFA (μmol/L)[(1)] | −0.463 | 0.0011 | 13.19 |
| GDM pregnant women | | | |
| BMI prepregnancy (kg/m$^2$) | 0.054 | 0.0022 | 13.7 |
| Newborns from control pregnancies | | | |
| Leptin (ng/mL)[(1)] | 0.571 | 0.0114 | 13.7 |
| Newborns from GDM pregnancies | | | |
| Leptin (ng/mL)[(1)] | 0.308 | 0.0001 | 14.9 |

Only significant regressions are shown; others were not significant ($P > 0.05$). Independent variables included were prepregnancy BMI, neonatal fat mass, birth weight, TAG[(1)], NEFA[(1)], glycerol[(1)], leptin[(1)], adiponectin[(1)], RBP4, and AFABP[(1)]. [(1)]Log-transformed for statistical comparisons.

In the absence of more evidence, it is only possible to speculate on the mechanism of AFABP effects on glucose metabolism in pregnancies and on how that mechanism is disrupted in pregnancies with GDM. AFABP in cord blood serum was found to correlate with both neonatal fat mass and leptin levels in GDM but not in control subjects. Based on the specific capacity of AFABP to bind fatty acids (6) it is assumed that when its concentration decreases in serum, as it was the case in cord blood of GDM subjects, the transport of NEFA to the liver must be compromised and their level consequently elevated. This is compatible with the decline in the other adipose tissue lipolytic product, glycerol, which is the preferred substrate for hepatic gluconeogenesis in newborns (18,19); gluconeogenesis should be increased where insulin resistance occurs.

Adipose tissue also produces other adipocytokines that have been reported to modulate the insulin response (20). Leptin concentration in cord serum was the only adipocytokine measured in this study that was associated with maternal HOMA in control subjects and GDM groups, but we failed to detect significant differences in its concentration between control and GDM mothers. However, we did observe that maternal, and, interestingly, cord serum of GDM subjects showed a marked hypoadiponectinemia compared with the control group. This result is consistent with the proposed role of adiponectin as an insulin-sensitizing factor during pregnancy and its decreased maternal (21) and fetal (22) concentrations in GDM pregnancies.

RBP4 concentrations were much higher (about 85% higher) in cord serum of GDM subjects than in the maternal circulation, and there was no correlation between the two measurements. In contrast the differences between control maternal serum, control cord serum, and GDM maternal serum were much smaller (Fig. 1). This suggests either that placental transport is less effective in GDM pregnancies with higher maternal concentrations required to achieve adequate fetal levels or that decreased degradation of the protein in GDM mothers results in the accumulation. Such an increase of RBP4 in GDM could contribute to the development of the insulin resistance, as has been reported in animal models (23). When compared with other adipocytokines, the number of reports on RBP4 in gestational diabetes is low; nevertheless, most of them report higher RBP4 levels in GDM women (24), as we did (Fig. 1). Studies of RBP4 in cord blood of GDM women are extremely scarce in the literature and do not show the same large differences from control subjects we report herein (25). Our findings on the low concentration of adiponectin and the high concentration of RBP4 found in women with GDM and their newborns are consistent with their higher insulin resistance.

In conclusion, our observations demonstrate the presence of AFABP in cord serum. We propose that its main source is fetal tissue. In GDM fetuses AFABP values correlate with markers of neonatal adiposity. Downregulation of adiponectin and upregulation of RBP4 in GDM mothers and their fetuses may be related to their insulin-resistant condition, whereas the changes in AFABP do not seem to be related.

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H.O.-S. performed biochemical determinations, interpretation of metabolic data, and statistical study and article writing. U.S.-G. collaborated in the experimental design, supported K.M., and undertook supervision and critical review of the manuscript. K.M. and M.A.-D. were responsible for the clinical recruitment, sample collection, storage preparation, and analysis of clinical histories. K.G. and U.K. measured cholesterol, TAG, and leptin. E.H. collaborated in the experimental design and undertook supervision and article-writing activities.

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