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Oxidant balance markers at birth in relation to glycemic and acid-base parameters

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Abstract

In diabetic pregnancies, suboptimal glycemic control is a risk factor for fetal acidemia and stillbirth. We hypothesized that the diabetic intrauterine milieu (hyperglycemia, hyperinsulinemia, changes in acid-base status) might predispose to oxidative stress. We studied 70 newborns whose mothers had pregestational diabetes (58 with type 1 diabetes mellitus) and 71 control newborns from nondiabetic mothers. Protein carbonyls (PCs), malondialdehyde, and 8-hydroxy-2′deoxyguanosine were measured in umbilical vein plasma as a reflection of protein, lipid, and DNA oxidative damage, respectively; glutathione peroxidase–3 (GPx3), an important circulating antioxidant enzyme, was also assayed. Despite satisfactory glycemic control in the majority of diabetic mothers, their newborns showed higher birth weight and relative hyperglycemia, hyperinsulinemia, and respiratory acidemia. The oxidant balance marker concentrations were not different at the $P < .05$ level between the 2 groups, and there was no relationship to maternal hemoglobin A_{1C} levels in the diabetic group. However, in the entire sample, increasing glucose levels at birth were related to lower GPx3 and higher PC concentrations; and GPx3 and PC concentrations were inversely correlated. In addition, a depressed pH or larger base-deficit at birth was related to higher PC and 8-hydroxy-2′deoxyguanosine concentrations. In conclusion, oxidant balance markers at birth are not affected by maternal diabetes per se and its long-term glycemic control, yet some markers are acutely tuned to metabolic cues including glucose and the acid-base environment.

1. Introduction

The Saint Vincent declaration (1989) set targets to "achieve pregnancy outcome in the diabetic woman that approximates that of the nondiabetic woman" [1]. Yet the perinatal mortality rate remains 3-fold higher in pregnancies complicated by pregestational diabetes mellitus [2,3]. Stillbirths account for the majority of perinatal deaths, but many stillbirths are unexplained apart from suboptimal glycemic control [4,5]. A cordocentesis study in fetuses of diabetic mothers demonstrated a relationship between higher maternal hemoglobin (Hb) A_{1C} levels and fetal acidemia [6]. Experimentally, a chronic glucose infusion in ovine fetuses resulted in augmented tissue oxygen consumption and arterial hypoxemia [7].

Mitochondrial dysfunction and oxidant generation might partly explain the increased risk of stillbirth. Hyperglycemia triggers the accumulation of reactive oxygen species in adipocytes [8]. Diabetes in adults is associated with oxidative damage to lipids, proteins, and DNA [9-12], which may result in part from down-regulation of enzymatic antioxidant defense systems such as glutathione peroxidase (GPx) [9,13]. Increased lipid peroxidation was also observed in diabetic gravidas [14], and there is evidence for a link between oxidative damage and congenital malformations in diabetic pregnancies [15].

In the current study, we measured oxidant balance markers in umbilical vein (UV) plasma of newborns of mothers with pregestational diabetes. In particular, we sought to examine the relationship between these markers and maternal/newborn glycemic parameters as well as size and acid-base parameters at birth. Three oxidation products were assayed: protein carbonyls (PCs), formed in part by oxidation of amino acid side-chains; malondialdehyde (MDA), a highly toxic by-product formed in part by lipid

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oxidation–derived free radicals; and 8-hydroxy-2′-deoxyguanosine (8-OH-dG), produced by oxidant-induced enzymatic cleavage after 8-hydroxylation of the guanine base and therefore a measure of DNA oxidative damage. In addition, we measured GPx3, the only one of the 5 GPx isoforms that can be quantified in the circulation, which is down-regulated in adult diabetes [13,16].

2. Subjects and methods

2.1. Subjects

This case-control study was approved by the faculty of medicine ethical committee, and consent was obtained from the participating mothers. Case umbilical cord blood samples were obtained at 70 of 71 consecutive live births from mothers with pregestational diabetes who delivered at our center between December 2004 and June 2009. Of these, 58 mothers had type 1 diabetes mellitus (White classification: 12 class B, 29 class C, 9 class D, 2 class R, 3 class F, and 3 class FR) and 12 had type 2 diabetes mellitus. Fifty-six gravidas (54 with type 1 and 2 with type 2 diabetes mellitus) were treated with continuous subcutaneous insulin infusion (47/56 started before pregnancy); the others were treated with multiple insulin injections. We recorded all HbA_{1C} levels sampled in the first (≤14 weeks gestational age [GA]), second (15-28 weeks GA), and third (≥29 weeks GA) trimester and calculated mean trimester values; the last HbA_{1C} level (in all cases <4 weeks before delivery) was also recorded. Hemoglobin A_{1C} was measured by reversed-phase cation exchange chromatography (ADAMS HA-8160, Menarini Diagnostics Benelux, Zaventem, Belgium; normal values are 4.0% to 6.0%. Our policy for diabetic patients is delivery at 38 to 39 weeks, but some women deliver earlier or the pregnancy is terminated because of complications (eg, hypertension). Control cord blood samples were obtained from nondiabetic mothers who delivered at a similar GA during the duty calls of one of us (JV). We recorded whether the mothers received betamethasone before preterm birth (Celestone, Schering-Plough, Kenilworth, NJ; 2 injections of 12 mg intramuscularly) and whether there had been clinical labor (regular uterine contractions with or without ruptured membranes) before delivery. Other clinical parameters are shown in Table 1.

Predelivery glycemic management in the diabetic parturients consisted of adjusted glucose (100 g/L) and insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark; 50 IU in 100 mL NaCl 0.9%) infusions started before elective cesarean delivery (fasting condition, no morning insulin bolus) or when clinical labor was diagnosed. No further intravenous glucose was given during labor with oxytocin administration or spinal/epidural anesthesia, but oral intake of liquids and food was allowed. Blood glucose was monitored hourly and maintained between 80 and 120 mg/dL (4.4-6.7 mmol/L). In the nondiabetic parturients, a starch-containing colloid solution (Voluven 6%, Fresenius Kabi, Bad Homburg, Germany) was infused before elective cesarean delivery (fasting condition). During labor, oxytocin (if needed) was given in a glucose solution (50 g/L); oral intake was allowed.

Umbilical artery (UA) and UV blood samples were obtained immediately after delivery with heparin-containing syringes, and blood gases (pH, PO_2, O_2 saturation, PCO_2, HCO_3^-, and base excess/deficit) were analyzed within minutes using an ABL 700 Analyzer (Radiometer Medical, Brønshøj, Denmark). An additional blood sample was obtained by a 20-mL syringe for clinical requirements and this study. The samples were centrifuged (3000 rpm, 10 minutes, 4°C) as rapidly as possible, and the plasma was stored in aliquots at −80°C until analysis in a single batch.

Table 1
Maternal and neonatal data

	Control (n = 71)	Diabetes (n = 70)	
Mothers			
Age at delivery (y)	31 ± 0.5	31 ± 0.6	.84*
Parity (n (%) nulliparous)	31 (44%)	39 (56%)	.31†
Height (cm)	166 ± 0.9	167 ± 0.9	.63*
BMI at 1st antepartumvisit (kg/m^2)	25.4 ± 0.7	26.8 ± 0.6	**.033***
Gestational weight gain (kg)	12.2 ± 0.7	13.2 ± 0.7	.49*
Hypertension, n (%)	26 (37%)	27 (39%)	.81†
Smoking, n (%)	6 (8%)	8 (11%)	.57†
Received betamethasone, n (%)	7 (10%)	3 (4%)	.20†
Clinical labor, n (%)	38 (54%)	39 (56%)	.79†
Mean HbA_{1C} 2nd trimester (%)		6.1 ± 0.08	
Mean HbA_{1C} 3rd trimester (%)		6.3 ± 0.06	
Last HbA_{1C} before delivery (%)		6.3 ± 0.07	
Newborns at birth			
Female sex, n (%)	29 (41%)	33 (47%)	.45†
Born vaginally, n (%)	31 (44%)	26 (37%)	.43†
GA (wk)	36.7 ± 0.2	36.8 ± 0.2	.82*
Weight (g)	2977 ± 77	3360 ± 84	**<.001***
Weight SD score	0.19 ± 0.11	1.06 ± 0.15	**<.001***
Length (cm)	48.9 ± 0.4	49.4 ± 0.4	.073*
Ponderal index (g/cm^3)	2.57 ± 0.03	2.75 ± 0.04	**<.001***
Head circumference (cm)	34.0 ± 0.2	34.2 ± 0.3	.32*
UA[a] pH	7.29 ± 0.008	7.26 ± 0.008	**.003**
PO_2 (kPa)	2.38 ± 0.09	2.25 ± 0.09	.27*
O_2 saturation (%)	21.8 ± 1.7	18.7 ± 1.6	.14*
PCO_2 (kPa)	7.06 ± 0.14	7.84 ± 0.17	**<.001***
HCO_3^- (mmol/L)	21.3 ± 0.3	21.8 ± 0.4	.38*
Base excess (nmol/L)	−1.4 ± 0.3	−1.6 ± 0.3	.62*
(UA-UV) PCO_2 (kPa)	1.16 ± 0.11	1.39 ± 0.13	.18*
UV glucose (mmol/L)	4.14 ± 0.12	5.35 ± 0.25	**<.001***
Insulin (pmol/L)	35 ± 4	163 ± 22	**<.001***
Total protein (g/L)	62.2 ± 1.0	55.8 ± 1.2	**<.001***
PC (μg/mg protein)	0.79 ± 0.03	0.88 ± 0.04	.16*
MDA (nmol/L)	0.3 ± 0.02	0.3 ± 0.02	.81*
8-OH-dG (ng/mL)	10.57 ± 0.25	10.49 ± 0.26	.72*
GPx3 (ng/mL)	1425 ± 77	1335 ± 69	.19*

Data are shown as means ± SEM or number (percentage). The UV data were back-transformed for clarity.

[a] Umbilical vein blood gases are not shown. The r value was .82 for UA and UV pH data, .61 for UA and UV PO_2, .63 for UA and UV O_2 saturation, .68 for UA and UV PCO_2, .88 for UA and UV HCO_3^-, and .89 for UA and UV base excess (all Ps < .001).

* P value obtained by 2-sample test.

† P value obtained by χ^2 test.

2.2. Assays

Glucose was measured by the glucose-oxidase method with a YSI 2300 Stat Plus Glucometer (YSI, Yellow Springs, OH); the coefficient of variation is 1.2%. Insulin was assayed using an ultrasensitive enzyme immunoassay (Mercodia, Uppsala, Sweden) with a detection limit at 0.07 mU/L (0.42 pmol/L) and within- and between-assay variation of less than 5.4%. Total protein was measured colorimetrically in duplicate (Pierce BCA protein kit, Rockford, IL). Protein carbonyls were measured in duplicate by enzyme immunoassay using the standard procedure (Biocell PC test; Alexis, Lausen, Switzerland); the assay variation is 5% to 15% depending on the PC concentration. Malondialdehyde was determined by third-derivative analysis from spectrophotometric scans (400-700 nm) (Northwest Life Sciences, Vancouver, WA); the useful range is between 0.1 and 10 μmol/L. 8-Hydroxy-2′-deoxyguanosine was measured in triplicate, as recommended by the manufacturer, by enzyme immunoassay (ACE; Cayman Chemical, Ann Arbor, MI); the detection limit is 33 pg/mL, and the assay variation is less than 11.7%. Glutathione peroxidase–3 was determined by enzyme immunoassay (AdipoGen, Seoul, Korea); the detection limit is 100 ng/L, and the assay variation is less than 9.65%. Average values were calculated from duplicate or triplicate measurements.

2.3. Data analysis

We used the NCSS software, version 2004 (Kaysville, UT). The birth weight SD score was computed as (actual − mean) birth weight/SD for each GA week [17]. The glucose, insulin, PC, MDA, 8-OH-dG, and GPx3 data were log-transformed before analysis to achieve normal (glucose, insulin, homeostasis model assessment index, PC, 8-OH-dG, GPx3) or improved (MDA) distribution in the diabetic and control groups (Kolmogorov-Smirnov test). We used the χ^2 test for comparisons of categorical variables between 2 groups. For comparisons of continuous variables between 2 groups, we checked for normality (omnibus normality) and variance (modified Levene equal variance test) and then used the appropriate 2-sample test (equal variance *t* test, Aspin-Welch unequal variance test, Mann-Whitney *U* test, Kolmogorov-Smirnov test). One-way analysis of variance was used for comparisons of continuous variables between 3 groups; if $P < .05$, the individual groups were compared by Tukey-Kramer multiple-comparison test. For regression analysis, we used Pearson correlation coefficients. Multiple regression analysis was performed using Huber robust regression.

3. Results

3.1. Effects of maternal diabetes on oxidant balance markers at birth

Gravidas with pregestational diabetes showed a higher body mass index (BMI) at the first antepartum visit than controls, but all other pregnancy characteristics were comparable (Table 1). The last HbA_{1C} level before delivery was less than 7.0% in 62 (89%) and less than 6.5% in 50 (71%) diabetic women. Gravidas with type 2 diabetes mellitus were older ($P < .001$) and shorter ($P = .038$) and showed a higher BMI ($P < .001$) than those with type 1 diabetes mellitus, but their HbA_{1C} levels were not different (data not shown).

Birth weight was 13% higher in the diabetic group, and the ponderal index was also increased. Umbilical artery blood pH was lower, whereas PCO_2 was higher, in the diabetic group. Newborns of diabetic mothers showed 29% higher UV plasma glucose and 10% lower total protein concentrations, and their insulin concentrations were 4.7-fold higher than in controls. Size measurements, blood gases, and plasma glucose-insulin concentrations at birth were comparable ($P > .20$) between type 1 and type 2 diabetes mellitus subjects (data not shown).

There were no significant differences in UV PC, MDA, 8-OH-dG, or GPx3 concentrations between newborns of diabetic mothers and controls; however, there was a trend for PC to be higher and GPx3 to be lower ($P < .20$) in the diabetic group. No significant differences were found in the oxidant balance markers between newborns of mothers with type 1 or type 2 diabetes mellitus, although there was a tendency for MDA levels to be higher ($P = .086$) and for GPx3 to be lower ($P = .12$) in newborns of type 2 vs type 1 diabetes mellitus mothers. In the diabetic group, none of the oxidative stress parameters at birth was related to the maternal HbA_{1C} level at any trimester of pregnancy (data not shown). Furthermore, the *r* between the last recorded HbA_{1C} level and UV PC was −.007 ($P = .95$); and similar results were obtained for MDA ($r = .11$, $P = .33$), 8-OH-dG ($r = −.17$, $P = .17$), and GPx3 ($r = .04$, $P = .70$).

3.2. Effects of labor and mode of birth on oxidant balance markers

Gestational age and weight at birth were comparable in labor-exposed and nonexposed newborns, but the ponderal index of labor-exposed neonates was lower ($P = .004$). Labor-exposed newborns showed a less favorable acid-base profile (lower UA and UV pH, HCO_3^-, and base excess; lower UV PO_2 and O_2 saturation; all *P*s < .006), and higher glucose (5.0 ± 0.2 vs 4.44 ± 0.22 mmol/L, $P = .023$) but lower insulin concentrations ($P = .02$). Similar differences regarding acid-base and glucose-insulin characteristics were observed between newborns delivered vaginally vs abdominally (data not shown).

Protein carbonyl concentrations were 19% higher in labor-exposed vs nonexposed neonates (0.90 ± 0.04 vs 0.75 ± 0.04 μg/mg protein, $P = .005$); and 8-OH-dG tended to be higher as well ($P = .095$), although there was no difference for MDA and GPx3 (both *P*s > .20). There were no significant differences in PC ($P = .11$), MDA ($P = .29$), 8-OH-dG ($P = .97$), and GPx3 ($P = .90$) concentrations according to the mode of birth (vaginally vs abdominally).

3.3. Regression analyses in entire cohort

3.3.1. Individual oxidant balance markers

Protein carbonyls and GPx3 were inversely correlated ($r = -.36$, $P < .001$), and there was also a trend for a correlation between PCs and MDA ($P = .079$) or 8-OH-dG ($P = .19$).

3.3.2. Oxidant balance and clinical parameters at birth

None of the oxidant balance markers was different between girls and boys (*t* tests: all *P*s > .20). Malondialdehyde was inversely correlated with GA ($r = -.18$, $P = .038$) and birth weight ($r = -.24$, $P = .005$) and length ($r = -.20$, $P = .027$); but no such correlations were observed for PC, 8-OH-dG, or GPx3 (data not shown).

3.3.3. Oxidant balance and glucose- insulin concentrations at birth

Protein carbonyl was related to both glucose ($r = 0.25$, $P = .003$) and insulin ($r = .18$, $P = .034$), whereas GPx3 was inversely related to glucose ($r = -.19$, $P = .028$) but not insulin ($P > .20$). Malondialdehyde and 8-OH-dG were not related to these metabolic parameters ($P > .20$). Stratification of the newborns into tertiles according to their glucose level at birth (Table 2) showed raised PC concentrations in the highest tertile and depressed GPx3 in the middle and highest tertile compared with the lowest tertile. In addition, pH and base excess were reduced with higher glucose levels.

3.3.4. Oxidant balance and acid-base status at birth

The correlations were controlled for GA because GA affects blood gas parameters [18]. Protein carbonyl was correlated at the $P < .05$ level with UA and UV pH and UA base excess; 8-OH-dG was correlated with UA and UV pH, UV PO_2, UA and UV O_2 saturation, UA and UV PCO_2, and UA base excess; and GPx3 was correlated with UA O_2 saturation and UA and UV HCO_3^-. Malondialdehyde was not related to any acid-base parameter. Stratification of the newborns into tertiles according to their pH level at birth (Table 3) showed higher PC and 8-OH-dG concentrations in the lowest compared with the highest tertile.

3.3.5. Multiple regression analyses

We included independent variables identified through the above analyses and antenatal betamethasone on the basis of a previous study [17]. Table 4 shows that PC concentrations were predicted by glucose levels and exposure to labor, whereas MDA was predicted by the presence of type 2 diabetes mellitus and birth weight. 8-Hydroxy-2′-deoxyguanosine concentrations were predicted by pH values at birth and also by antenatal betamethasone administration and glucose levels; GPx3 was predicted by GA, glucose levels, birth weight, antenatal betamethasone, and pH values.

4. Discussion

We documented that maternal diabetes does not affect the plasma concentrations of protein (PC) and DNA (8-OH-dG) oxidation products or the concentrations of the GPx3 antioxidant enzyme in their newborns at birth (Table 1). In addition, we found no correlation between the maternal HbA_{1C} level and any oxidation marker at birth. These findings provide reassurance to diabetic gravidas that there is no evidence of accumulative oxidative damage in the fetus. However, PC, 8-OH-dG, and GPx3 were related to a number of clinical and biochemical parameters including recent betamethasone treatment, labor, and glucose and pH levels at birth. Acute tuning to the glycemic and acid-base environment is not surprising given the short half-life of oxidants and antioxidants [12]. Our results are in agreement with data obtained in individuals with type 2 diabetes mellitus showing

Table 2
Oxidant balance markers according to glucose concentration in UV plasma

	Tertile 1 Glucose 1.59-3.84 mmol/L (n = 47)	Tertile 2 Glucose 3.85-5.15 mmol/L (n = 47)	Tertile 3 Glucose 5.20-12.93 mmol/L (n = 46)	ANOVA *P*	χ^2 *P*
Maternal diabetes mellitus (yes)	16 (34%)	22 (47%)	32 (70%)		**.002**
Labor (yes, %)	18 (38%)	31 (66%)	27 (59%)		**.02**
UA pH	7.30 ± 0.008	7.27 ± 0.011	7.25 ± 0.009*	**.008**	
PO_2 (kPa)	2.33 ± 0.10	2.25 ± 0.13	2.37 ± 0.11	.79	
PCO_2 (kPa)	7.12 ± 0.18	7.49 ± 0.20	7.72 ± 0.19	.089	
Base excess (mmol/L)	−0.9 ± 0.3	−1.4 ± 0.3	−2.2 ± 0.4*	**.021**	
UV					
Insulin (pmol/L)	52 ± 6	65 ± 13	175 ± 31†	**<.001**	
Total protein (g/L)	61.7 ± 1.4	58.9 ± 1.3	56.3 ± 1.5*	**.024**	
PC (μg/mg protein)	0.74 ± 0.04	0.85 ± 0.05	0.91 ± 0.05*	**.044**	
MDA (nmol/L)	0.3 ± 0.02	0.3 ± 0.02	0.3 ± 0.01	.97	
8-OH-dG (ng/mL)	10.78 ± 0.32	10.56 ± 0.31	10.24 ± 0.31	.45	
GPx3 (ng/L)	1614 ± 85	1336 ± 93*	1185 ± 82*	**.001**	

Data are shown as number (percentage) or means ± SEM. The UV data were back-transformed for clarity.

* Significant difference with tertile 1.

† Significant difference with tertiles 1 and 2.

Table 3
Oxidant balance markers according to pH in UA blood

	Tertile 1 pH 7.045-7.25 (n = 47)	Tertile 2 7.253-7.309 (n = 45)	Tertile 3 7.31-7.456 (n = 45)	ANOVA *P*	χ^2 *P*
Maternal diabetes mellitus	28 (60%)	26 (58%)	13 (29%)		**.005**
Labor	37 (79%)	21 (47%)	18 (40%)		**<.001**
UA					
PO_2 (kPa)	1.98 ± 0.08	2.20 ± 0.10	2.79 ± 0.13*	**<.001**	
PCO_2 (kPa)	8.62 ± 0.16	7.38 ± 0.10†	6.25 ± 0.11*	**<.001**	
Base excess (mmol/L)	−2.8 ± 0.4	−1.2 ± 0.3†	−0.4 ± 0.3†	**<.001**	
UV					
Glucose (mmol/L)	5.4 ± 0.3	4.6 ± 0.3†	4.1 ± 0.2†	**<.001**	
Insulin (pmol/L)	98 ± 16	122 ± 31	68 ± 14	.13	
Total protein (g/L)	60.1 ± 1.5	57.7 ± 1.4	58.8 ± 1.5	.53	
PC (μg/mg protein)	0.92 ± 0.05	0.84 ± 0.06	0.74 ± 0.04†	**.018**	
MDA (nmol/L)	0.3 ± 0.01	0.3 ± 0.02	0.3 ± 0.02	.66	
8-OH-dG (ng/mL)	11.22 ± 0.33	10.42 ± 0.34	9.88 ± 0.25†	**.018**	
GPx3 (ng/L)	1430 ± 90	1443 ± 95	1289 ± 90	.32	

Data are shown as number (percentage) or means ± SEM. The UV data were back-transformed for clarity.
* Significant difference with tertiles 1 and 2.
† Significant difference with tertile 1.

that the lipid peroxidation marker 8-*iso*-prostaglandin $F_{2\alpha}$ is related to diurnal glycemic excursions but not the HbA_{1C} level [19]. Therefore, glucose peaks should be avoided as much as possible in normal and diabetic pregnancies.

Measurement of oxidant balance markers in UV plasma is feasible. Malondialdehyde concentrations were low but quantifiable (0.1-0.9 μmol/L); in a previous study using the same methodology, we found MDA levels of up to 1.6 μmol/L in newborns recently treated with betamethasone [17]. Protein carbonyl concentrations measured by the same assay were substantially higher in UV than in adult plasma [20]. The concentrations of 8-OH-dG were within the range reported for adults [21]. Finally, circulating GPx3 concentrations in healthy adults were reported to be 2250 to 2500 ng/mL with the same assay [13], that is less than 2-fold higher than in UV plasma. In contrast, the well-established dROMS assay [22] did not yield reliable results in UV plasma (Verhaeghe, Van Herck, van Bree; unpublished data).

Oxidant balance markers were measured in UV rather than UA plasma. Although the UA reflects the fetal compartment better than does the UV, we opted for the latter largely for technical reasons. In addition, UA and UV blood gas values were well correlated. Umbilical artery and UV plasma concentrations of insulin-like growth factor binding protein–1, another blood gas–dependent marker, also showed an *r* value of .98 [23].

Blood gas analysis showed that newborns of diabetic mothers had lower pH and higher PCO_2 but normal HCO_3^- values in both UA and UV, compatible with "respiratory" acidemia [24]. An increase in fetal CO_2 load (ie, arteriovenous PCO_2 difference) related to weight accrual appears to be responsible for the increment in UA PCO_2 between 37

Table 4
Multiple regression analysis of oxidant balance markers in UV plasma at birth

Independent variables	Dependent variables			
	UV PC	MDA	8-OH-dG	GPx3
Intercept	*P* = .78	*P* = .73	*P* < .001 (*t* value = 8.25)	*P* < .001 (*t* value = 3.98)
Maternal diabetes mellitus				
Type 1 diabetes mellitus (vs no)	*P* = .70	*P* = .50	*P* = .92	*P* = .24
Type 2 diabetes mellitus (vs no)	*P* = .13	*P* = .009 (*t* value = 2.66)	*P* = .15	*P* = .67
Antenatal betamethasone	*P* = .24	*P* = .087	*P* = .005 (*t* value = 2.83)	*P* = .005 (*t* value = −2.88)
Labor (vs no)	*P* = .045 (*t* value = 2.02)	*P* = .987	*P* = .14	*P* = .12
GA	*P* = .49	*P* = .23	*P* = .12	*P* < .001 (*t* value = 3.39)
Birth weight	*P* = .80	*P* = .016 (*t* value = −2.43)	*P* = .44	*P* = .004 (*t* value = −2.92)
UA pH	*P* = .36	*P* = .99	*P* = .002 (*t* value = −3.21)	*P* = .005 (*t* value = −2.87)
UV glucose	*P* = .012 (*t* value = 2.56)	*P* = .28	*P* = .033 (*t* value = −2.15)	*P* = .001 (*t* value = −3.36)
Total model R^2	.202	.144	.183	.223
P value of model	<.001	.013	<.001	<.001
n	135	131	136	135

and 43 weeks GA [18]. However, we found a comparable arteriovenous PCO_2 difference in both newborn groups (Table 1) and no correlation between UA, UV, or (UA-UV) PCO_2 and birth weight or weight SD score ($P > .197$, data not shown). Another possibility is that the respiratory acidemia in newborns of diabetic mothers is related to a repressed fetomaternal CO_2 exchange across the placenta or/and membranes, perhaps as a result of accelerated aging [18]. Further studies are needed to clarify gas exchange between mother and fetus in diabetic pregnancies.

Exposure to labor affected the acid-base environment, as expected, but also raised glucose (+13%) and PC concentrations (+19%) in UV plasma. In our delivery unit, as in many others, a restrictive nutritional policy before elective cesarean delivery (fasting, no glucose load) contrasts with a more liberal policy during labor. Indeed, labor is considered to be a form of exercise with a substantial increase in glucose requirement [25]. In our diabetic parturients, oral intake of fluid and food was allowed; but euglycemia was maintained by an adjusted insulin drip. In the controls, the infused amount of glucose was small (only when oxytocin infusion was needed; ie, generally <25 g). Glucose 10% infusion (80-100 g) during labor raised maternal [26] and newborn [27] glucose concentrations, whereas UA pH levels tended to decrease ($P < .15$) [27]. Our data showed a gradual drop in pH and base excess in newborns with increasing glucose concentration (Table 2). Therefore, the effects of glucose 10% infusions or, for that matter, oral carbohydrate drinks [28] during labor on neonatal oxidant balance and proinflammatory markers deserve careful study; we consider clinical implementation premature at this stage. Furthermore, the use of an adjusted insulin drip in diabetic parturients is endorsed by the current study.

We have previously documented that antenatal betamethasone administration has profound and acute (ie, within 24 hours) effects on GPx3 and MDA concentrations at birth in newborns less than 34 weeks GA [17]. Only 10 of 141 newborns in this study received antenatal betamethasone because only 12 of 141 were born before 34 weeks GA; glucocorticoids are also avoided if possible in diabetic pregnancies because of a detrimental effect on maternal glycemic control. Despite small numbers, antenatal betamethasone was confirmed as a correlate of GPx3 (down-regulation), and 8-OH-dG and MDA (up-regulation) at birth (Table 4).

Table 4 shows a significant effect of type 2 diabetes mellitus and birth weight on MDA concentrations at birth. However, the number of type 2 diabetes mellitus cases was small (12/141); therefore, a definitive conclusion remains elusive. Type 2 diabetes mellitus gravidas showed a higher BMI than type 1 diabetes mellitus subjects, but birth weight was not different. Increased lipid peroxidation has been reported in obese individuals [22]. It might be interesting to relate UV MDA levels to newborn fat content.

Much remains to be learned about the oxidant balance in fetal life and during labor, and results are not always concordant between studies. Glutathione peroxidase–3 appears to be the most sensitive marker, although all oxidant marker regression models showed a rather low total R^2 value (.14-.22) (Table 4). This may be explained by the short half-life of oxidants, assay limitations [12], our prudent labor policy (eg, no UA pH values <7.0; adjusted insulin drip in diabetic gravidas), or/and inadequate knowledge about factors that drive oxidative processes during fetal life and labor. Nonetheless, the current data are the first to identify glucose and the acid-base environment as parameters to which some oxidant balance markers are tuned at birth.

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