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Maternal and Umbilical Cord Blood Redox Status in Gestational Diabetes Mellitus: A Case–Control Study in Humans

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Abstract

Gestational diabetes mellitus (GDM) is associated with maternal oxidative stress, but its relationship with fetal redox status is unclear. In this exploratory case–control study, maternal serum was obtained on admission for cesarean delivery under regional anesthesia and umbilical cord blood at delivery from 65 women with GDM (34 diet-managed, 31 insulin-treated) and 65 normoglycemic controls. Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), oxidized low-density lipoprotein (ox-LDL), lipoprotein(a) and lipids were measured. Adjusted models included maternal age, body mass index (BMI) and parity. Maternal TOS (median 114.70 vs. 44.40 μmol H_2O_2 equiv./L; $p = 0.019$) and triglycerides ($p = 0.021$) were higher in GDM, whereas maternal TAS and OSI did not differ significantly. No significant differences in cord TAS, TOS or OSI were detected, but cord ox-LDL was higher in GDM (35.93 vs. 26.61 U/L; $p = 0.009$). After adjustment these differences were attenuated, and maternal BMI was associated with cord ox-LDL (4.0% higher per 1 kg/m^2; $p = 0.006$). No group difference remained significant after Holm correction. Maternal and cord TAS were correlated ($\rho = 0.37$; $p < 0.001$), whereas no significant correlation was detected for TOS. These exploratory findings require confirmation in prospective studies.

Keywords: gestational diabetes mellitus; oxidative stress; total antioxidant status; total oxidant status; oxidative stress index; oxidized LDL; umbilical cord blood; lipoprotein(a)

1. Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance first recognized during pregnancy, is one of the most common metabolic complications of gestation and carries short- and long-term consequences for both mother and offspring [1,2]. Adverse perinatal outcomes increase continuously with maternal glycemia [3], and in women with GDM, higher pre-pregnancy BMI has been associated with adverse outcomes independently of age and gestational weight gain [4].

Oxidative stress, an imbalance between the production of reactive oxygen species and antioxidant defenses, has been implicated in the pathophysiology of GDM and its complications [5,6]. The placenta is both a source and a target of oxidative stress [7], and it stands between maternal and fetal circulations. Whether the maternal oxidative burden of GDM is transmitted to, buffered by, or independently generated within the fetoplacental unit therefore has implications for fetal metabolic programming.

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Relatively few studies have examined maternal and fetal compartments together in GDM [8–10], and the available evidence on oxidative stress biomarkers in maternal plasma, umbilical cord and placenta has recently been compiled in a systematic review and meta-analysis [11]. Biri et al. evaluated oxidant status in maternal plasma, cord plasma and placental tissue in GDM [8], and Şimşek et al. compared total antioxidant and total oxidant status in serum, saliva and gingival crevicular fluid between women with GDM and controls [12]. More recently, Chelu et al. found higher maternal oxidative stress and lower maternal antioxidant capacity in GDM, but no difference in cord blood redox markers [10]. In that study, maternal blood was collected at 32–36 weeks of gestation; we obtained maternal and cord samples during the same delivery admission, examined maternal–cord correlations of TAS and TOS, and included ox-LDL and lipids in the marker panel. Maternal obesity, which frequently accompanies GDM, is itself associated with oxidative stress in the fetoplacental unit [13], and cord blood oxidized low-density lipoprotein (ox-LDL) has been linked to insulin sensitivity and beta-cell function in newborns [14].

The aim of this study was to compare global redox markers—total antioxidant status (TAS), total oxidant status (TOS) and the oxidative stress index (OSI)—together with ox-LDL, lipoprotein(a) [Lp(a)] and lipid parameters in paired maternal serum and umbilical cord blood samples from pregnancies with and without GDM to examine whether maternal and cord redox markers are correlated and to assess whether group differences persist after adjustment for maternal age, body mass index (BMI) and parity.

2. Materials and Methods

2.1. Study Design and Participants

This single-center, observational, case–control study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Selçuk University, Konya, Türkiye. A total of 130 singleton pregnancies were included: 65 women diagnosed with GDM formed the study group and 65 women with a normal glucose challenge test formed the control group. Women were enrolled before 28 weeks of gestation. To eliminate differences in oxidative stress related to the mode of delivery and anesthesia, only women delivered by cesarean section under regional anesthesia were included. Gestational age was determined by the last menstrual period and confirmed by first-trimester ultrasonography. Maternal BMI was calculated from weight and height measured at admission for delivery.

Exclusion criteria were smoking or alcohol use; type 1 or type 2 diabetes mellitus; vascular or inflammatory disease; cardiac, hepatic or renal disease; a diagnosis of hyperlipidemia; multiple pregnancy; fetal growth restriction (estimated fetal weight below the 10th percentile); abnormal Doppler findings; premature rupture of membranes; and delivery before 37 weeks of gestation. The control group consisted of women with normal glucose challenge test results whose pregnancies and deliveries were uncomplicated and who met none of the exclusion criteria.

2.2. Screening, Diagnosis and Treatment of GDM

A two-step screening approach was used in accordance with the recommendations of the American College of Obstetricians and Gynecologists [2]. A 50 g glucose challenge test (GCT) was performed at 24–28 weeks; women at high risk (previous GDM, previous macrosomia or intrauterine fetal death, or pre-pregnancy BMI ≥ 30 kg/m^2) were screened at their first visit and, if negative, rescreened at 24–28 weeks. Women with a 1 h GCT value ≥ 140 mg/dL underwent a 3 h 100 g oral glucose tolerance test (OGTT), and GDM was diagnosed when at least two values met or exceeded the Carpenter–Coustan thresholds (fasting 95, 1 h 180, 2 h 155 and 3 h 140 mg/dL) [15]. Women with a 1 h GCT value ≥ 200 mg/dL were diagnosed with GDM without further testing ($n = 24$); those with

values of 140–199 mg/dL underwent a 100 g OGTT and were diagnosed by the above criteria (n = 41).

Women with GDM first received medical nutrition therapy for 2 weeks with one fasting and three postprandial capillary glucose measurements per day. Daily energy intake was calculated according to BMI and limited to 1900–2400 kcal in women with obesity, with 30–40% complex carbohydrates, 20% protein and 40% fat. Insulin therapy was initiated when fasting glucose remained ≥95 mg/dL or when at least two postprandial values exceeded 140 mg/dL at 1 h or 120 mg/dL at 2 h despite diet. The total daily insulin dose was 0.7–1.0 IU/kg, using a combination of intermediate- and short-acting insulin, and was adjusted according to glucose control. Thirty-four women (52.3%) were managed with diet alone and 31 (47.7%) required insulin.

2.3. Sample Collection and Laboratory Analyses

Maternal venous blood was drawn from the antecubital vein on admission for delivery, and umbilical cord blood was collected at delivery. Residual maternal venous blood collected for routine clinical investigations on admission for delivery and residual umbilical cord blood obtained for neonatal blood group determination were used; no blood was drawn solely for research purposes. Samples were collected into plain gel-containing biochemistry tubes and centrifuged at 3000 rpm for 5 min, and the supernatant was aliquoted into Eppendorf tubes and stored at −80 °C until analysis. On the day of analysis, samples were thawed and vortexed. Sample collection and all laboratory measurements were completed in 2014, within the original study; for the present report, no new samples were collected and no new laboratory measurements were performed.

Ox-LDL was measured with a commercial enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) according to the manufacturer's protocol, using a Rayto RT-2100C microplate reader (Rayto Life and Analytical Sciences Co., Ltd., Shenzhen, China). Recorded values were converted to U/L using a constant factor of 6.561. Total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and Lp(a) were measured spectrophotometrically with Abbott reagents on an Architect c16000 analyzer (Abbott Laboratories, Abbott Park, IL, USA). TAS and TOS were measured with commercial kits (Rel Assay Diagnostics, Gaziantep, Türkiye) on the same analyzer, using the automated colorimetric methods developed by Erel [16,17]. TAS was expressed as mmol Trolox equivalent/L and TOS as μmol H_2O_2 equivalent/L. The OSI was calculated as TOS (μmol/L)/[TAS (mmol/L) × 1000] × 100 [17].

2.4. Statistical Analysis

For this report, the measurement data of the original study were statistically re-analyzed using non-parametric methods and complete-case analysis. Continuous baseline variables are presented as mean ± standard deviation and compared with Student's *t*-test; Apgar scores are presented as median (interquartile range, IQR) and compared with the Mann–Whitney *U* test; categorical variables were compared with the chi-square test. Because most biomarkers were right-skewed, biomarker data are presented as median (IQR) and compared with the Mann–Whitney *U* test. Maternal ox-LDL values at the highest reported value (131.22 U/L) and cord Lp(a) values at the lowest reported value (2.0 mg/dL) were retained as reported; because this pattern is compatible with censoring at the limits of the assay range, these markers were analyzed with rank-based methods and interpreted with caution. To assess confounding, log-transformed biomarker concentrations were entered into multivariable linear regression models with GDM status, maternal age, BMI and parity as covariates; exponentiated coefficients are reported as ratios of geometric means with 95% confidence intervals (CI), and heteroskedasticity-robust (HC3) standard

errors with normal-reference p values were examined as a sensitivity analysis. Correlations between paired maternal and cord values were assessed with Spearman's rank correlation coefficient (ρ); maternal and cord values were linked within the same patient record by protocol number. Because many markers were compared in two compartments without a pre-specified primary outcome, the analyses were considered exploratory; p values are presented without adjustment for multiplicity, and Holm-adjusted p values [18] for the 18 group comparisons are reported in the text. Holm correction was applied only to these 18 group comparisons; no multiplicity correction was applied to the regression and correlation analyses, which were interpreted as exploratory. A sensitivity analysis excluding the 24 women diagnosed on the basis of the GCT alone (41 GDM vs. 65 controls) was performed. A two-sided $p < 0.05$ was considered nominally significant. Analyses were performed in Python (pandas 3.0.5, SciPy 1.18.1, statsmodels 0.15.0).

2.5. Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Selçuk University Faculty of Medicine (approval no. 2014/141; 29 April 2014). Written informed consent was obtained from all participants.

2.6. Use of Generative Artificial Intelligence

The use of generative AI tools is described in the Acknowledgments.

3. Results

3.1. Characteristics of the Study Population

Maternal age, BMI, gravidity and parity were higher in the GDM group than in the control group (Table 1). Birth weight was higher in the GDM group (3298.54 ± 497.38 vs. 3132.08 ± 449.59 g; $p = 0.047$), whereas Apgar scores and neonatal sex distribution did not differ between groups. Of the women with GDM, 24 were diagnosed on the basis of a GCT value ≥ 200 mg/dL and 41 by OGTT; 34 were managed with diet and 31 with insulin.

Table 1. Maternal and neonatal characteristics of the study groups.

Variable	GDM (n = 65)	Control (n = 65)	*p*
Maternal age (years)	33.57 ± 5.94	28.94 ± 6.05	<0.001
BMI (kg/m^2)	31.53 ± 5.80	29.44 ± 4.59	0.024
Gravidity	3.25 ± 1.58	2.46 ± 1.35	0.003
Parity	1.89 ± 1.26	1.28 ± 1.13	0.004
Birth weight (g)	3298.54 ± 497.38	3132.08 ± 449.59	0.047
Apgar score, 1 min	8 (7–8)	8 (7–8)	0.221
Apgar score, 5 min	9 (8–9)	9 (8–9)	0.800
Female neonates, n (%)	33 (50.8)	32 (49.2)	0.861
GDM diagnosis: GCT ≥ 200 mg/dL/OGTT, n	24/41	—	—
GDM treatment: diet/insulin, n	34/31	—	—

Values are mean ± standard deviation (Student's *t*-test), median (interquartile range; Mann–Whitney *U* test) or n (%) (chi-square test). BMI, body mass index (at delivery); GCT, 50 g glucose challenge test; GDM, gestational diabetes mellitus; OGTT, 100 g oral glucose tolerance test.

3.2. Maternal Serum Redox Markers and Lipids

Maternal TOS was higher in women with GDM than in controls (median 114.70 vs. 44.40 μmol H_2O_2 equiv./L; $p = 0.019$), whereas no significant differences were detected for maternal TAS and OSI (Table 2). Maternal triglycerides were higher in the GDM group (221.50 vs. 183.00 mg/dL; $p = 0.021$); no significant differences were detected for total

cholesterol, HDL-C, LDL-C, Lp(a) or maternal ox-LDL ($p = 0.641$ for ox-LDL); and in 32 of 65 samples in each group, maternal ox-LDL was at the highest reported value (131.22 U/L).

Table 2. Maternal serum redox markers, ox-LDL, Lp(a) and lipids.

Marker	GDM	Control	*p*
TAS (mmol Trolox equiv./L)	1.30 (1.20–1.50)	1.40 (1.20–1.50)	0.708
TOS (μmol H_2O_2 equiv./L)	114.70 (43.30–162.60)	44.40 (15.80–143.10)	0.019
OSI (arbitrary units)	5.37 (2.04–14.71)	3.07 (1.31–11.92)	0.104
ox-LDL (U/L) [a]	123.44 (90.00–131.22)	128.33 (72.98–131.22)	0.641
Lp(a) (mg/dL)	20.30 (9.84–32.20)	16.30 (3.49–27.50)	0.058
Total cholesterol (mg/dL)	189.50 (157.75–230.25)	184.00 (146.00–216.00)	0.532
Triglycerides (mg/dL)	221.50 (167.25–274.25)	183.00 (143.75–229.00)	0.021
HDL-C (mg/dL)	48.00 (39.25–58.00)	46.00 (37.00–52.00)	0.328
LDL-C (mg/dL)	102.80 (79.85–131.15)	97.50 (83.40–124.45)	0.637

Values are median (interquartile range); *p* values are from the Mann–Whitney *U* test. [a] In 32 of 65 samples in each group, maternal ox-LDL was at the highest reported value (131.22 U/L), compatible with censoring at the upper end of the assay range. GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OSI, oxidative stress index; ox-LDL, oxidized low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status.

3.3. Cord Blood Redox Markers and Lipids

In cord blood, no significant differences in TAS, TOS or OSI were detected between the GDM and control groups (Table 3). Cord blood ox-LDL was higher in the GDM group (median 35.93 vs. 26.61 U/L; $p = 0.009$). No significant differences were detected for cord lipids or Lp(a); cord Lp(a) was at the lowest reported value (2.0 mg/dL) in 42 GDM and 35 control samples. After Holm correction for the 18 maternal and cord group comparisons, none of the differences remained statistically significant (adjusted $p = 0.320$ for maternal TOS, 0.344 for maternal triglycerides and 0.163 for cord ox-LDL).

Table 3. Umbilical cord blood redox markers, ox-LDL, Lp(a) and lipids.

Marker	GDM	Control	*p*
TAS (mmol Trolox equiv./L)	1.60 (1.50–1.70)	1.60 (1.40–1.80)	0.759
TOS (μmol H_2O_2 equiv./L)	15.60 (6.70–46.30)	16.70 (8.70–60.20)	0.350
OSI (arbitrary units)	0.93 (0.41–2.68)	1.33 (0.62–3.16)	0.240
ox-LDL (U/L)	35.93 (23.36–55.27)	26.61 (17.63–34.65)	0.009
Lp(a) (mg/dL) [a]	2.00 (2.00–2.38)	2.00 (2.00–3.20)	0.235
Total cholesterol (mg/dL)	60.00 (50.75–68.75)	56.50 (47.25–65.75)	0.363
Triglycerides (mg/dL)	34.00 (26.50–54.00)	34.00 (26.50–50.00)	0.927
HDL-C (mg/dL)	23.50 (18.25–26.75)	21.00 (18.00–26.00)	0.297
LDL-C (mg/dL)	27.80 (22.00–32.75)	26.80 (22.10–32.35)	0.601

Values are median (interquartile range); *p* values are from the Mann–Whitney *U* test. [a] Cord Lp(a) was at the lowest reported value (2.0 mg/dL) in 42 GDM and 35 control samples, compatible with censoring at the lower end of the assay range. GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OSI, oxidative stress index; ox-LDL, oxidized low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status.

3.4. Adjusted Analyses

After adjustment for maternal age, BMI and parity, the geometric mean of maternal TOS remained 51% higher in GDM, but the difference was no longer statistically significant (ratio 1.51; 95% CI 0.96–2.37; $p = 0.076$), and the adjusted difference in maternal triglycerides

was attenuated (ratio 1.21; 95% CI 0.94–1.57; $p = 0.144$) (Table 4). The difference in cord ox-LDL was likewise attenuated (ratio 1.33; 95% CI 0.98–1.79; $p = 0.065$), whereas maternal BMI was associated with cord ox-LDL in the same model (4.0% higher per 1 kg/m^2; 95% CI 1.1–6.9%; $p = 0.006$). With HC3 standard errors, point estimates were unchanged and p values were 0.109 for maternal TOS, 0.180 for maternal triglycerides and 0.041 for cord ox-LDL (95% CI 1.01–1.74). This observational association does not show a direct effect of maternal BMI on cord ox-LDL and may reflect unmeasured shared factors.

Table 4. Multivariable analysis of redox markers and triglycerides (GDM vs. control).

Outcome	Ratio GDM/Control (95% CI)	p	BMI, Ratio per kg/m^2 (95% CI)	p
Maternal TAS	0.98 (0.88–1.11)	0.795	0.998 (0.985–1.012)	0.797
Maternal TOS	1.51 (0.96–2.37)	0.076	1.021 (0.979–1.064)	0.337
Maternal OSI	1.39 (0.84–2.31)	0.197	1.024 (0.965–1.087)	0.431
Maternal triglycerides	1.21 (0.94–1.57)	0.144	0.985 (0.957–1.015)	0.328
Cord TAS	0.99 (0.93–1.07)	0.878	1.002 (0.995–1.008)	0.600
Cord TOS	0.79 (0.46–1.35)	0.381	1.016 (0.966–1.068)	0.531
Cord OSI	0.75 (0.45–1.26)	0.275	1.018 (0.971–1.067)	0.464
Cord ox-LDL	1.33 (0.98–1.79)	0.065	1.040 (1.011–1.069)	0.006

Linear regression of log-transformed outcomes on GDM status, maternal age, BMI and parity; exponentiated coefficients are ratios of geometric means. BMI, body mass index (at delivery); CI, confidence interval; GDM, gestational diabetes mellitus; OSI, oxidative stress index; ox-LDL, oxidized low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status.

3.5. Maternal–Cord Relationships

Maternal and cord TAS were positively correlated in the whole cohort ($\rho = 0.37$; $p < 0.001$), with similar coefficients in the control ($\rho = 0.38$; $p = 0.002$) and GDM ($\rho = 0.34$; $p = 0.016$) groups (Figure 1, Table 5). In contrast, no significant correlations were detected for TOS ($\rho = -0.12$; $p = 0.171$), OSI, ox-LDL or Lp(a). Among lipids, maternal and cord HDL-C were correlated in the GDM group ($\rho = 0.32$; $p = 0.027$) but not in the control group ($\rho = -0.01$); the difference between these group-specific coefficients was not formally tested. Maternal BMI was weakly correlated with cord ox-LDL ($\rho = 0.18$; $p = 0.041$).

Table 5. Spearman correlations between paired maternal serum and cord blood values.

Marker	All: ρ (p)	Control: ρ (p)	GDM: ρ (p)
TAS	0.37 (<0.001)	0.38 (0.002)	0.34 (0.016)
TOS	−0.12 (0.171)	−0.13 (0.310)	−0.08 (0.530)
OSI	−0.14 (0.144)	−0.19 (0.143)	−0.09 (0.515)
ox-LDL	−0.03 (0.741)	−0.05 (0.704)	−0.03 (0.831)
Lp(a)	0.00 (0.957)	0.10 (0.443)	−0.02 (0.895)
Total cholesterol	0.00 (0.965)	−0.11 (0.417)	0.09 (0.551)
Triglycerides	0.15 (0.161)	0.30 (0.057)	0.00 (0.976)
HDL-C	0.15 (0.128)	−0.01 (0.946)	0.32 (0.027)
LDL-C	0.09 (0.355)	0.05 (0.720)	0.15 (0.308)

GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OSI, oxidative stress index; ox-LDL, oxidized low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status.

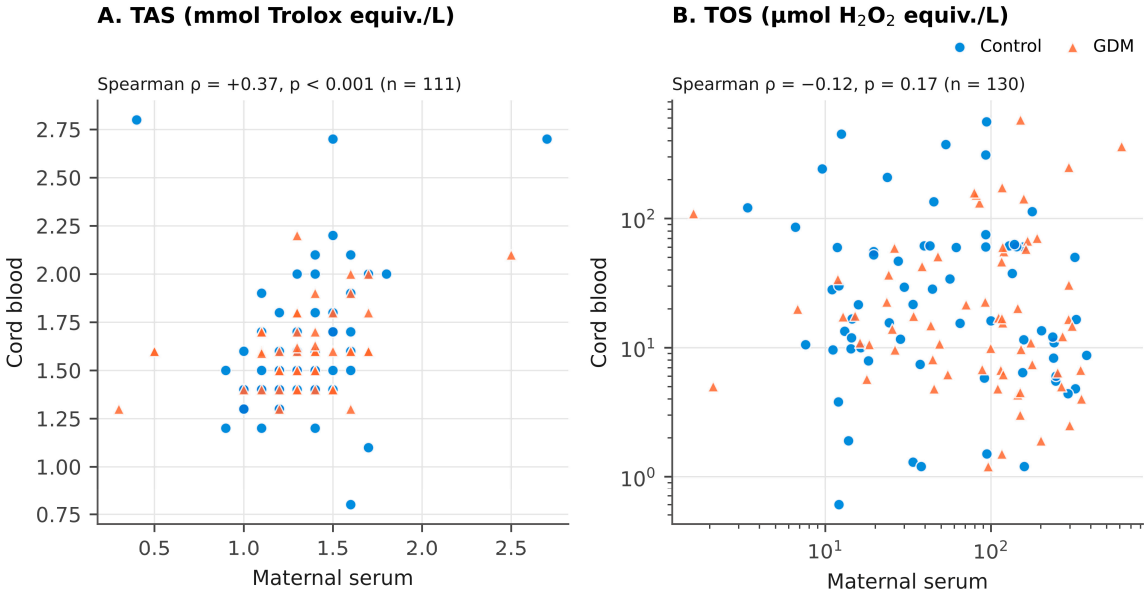

Figure 1. Relationship between maternal serum and umbilical cord blood (**A**) total antioxidant status (TAS) and (**B**) total oxidant status (TOS; logarithmic axes) in the control (circles) and gestational diabetes mellitus (GDM; triangles) groups. Spearman correlation coefficients refer to the whole cohort. The legend in panel (**B**) applies to both panels; overlapping points may conceal individual observations.

3.6. Sensitivity Analysis

In the sensitivity analysis restricted to women diagnosed by OGTT, the maternal TOS difference persisted (median 117.70 vs. 44.40 µmol H_2O_2 equiv./L; $p = 0.016$), whereas the differences in maternal triglycerides ($p = 0.060$) and cord ox-LDL (median 31.53 vs. 26.61 U/L; $p = 0.138$; adjusted ratio 1.20, $p = 0.303$) were attenuated; maternal BMI remained associated with cord ox-LDL ($p = 0.031$), and the maternal–cord TAS correlation was similar ($\rho = 0.34$).

4. Discussion

In this case–control study of paired maternal and umbilical cord samples, women with GDM had nominally higher maternal TOS and triglycerides than normoglycemic controls, whereas no significant differences were detected for TAS and OSI. In cord blood, no significant differences in global redox markers were detected between groups, but ox-LDL was nominally higher in neonates of mothers with GDM. After adjustment for maternal age, BMI and parity, these differences were attenuated, none remained significant after Holm correction, and maternal BMI was associated with cord ox-LDL in the adjusted model. Maternal and cord TAS values were positively correlated, whereas no significant correlation was detected for TOS.

The higher maternal TOS in GDM is consistent with the view that hyperglycemia and insulin resistance shift maternal redox balance toward oxidant predominance [5,6]. Chelu et al. found both higher oxidative stress and lower antioxidant capacity in maternal blood in GDM [10]. Results of studies measuring TAS and TOS in maternal serum have not been consistent; for example, Şimşek et al. reported lower serum TAS and TOS in women with GDM [12]. In our cohort, no significant difference in maternal TAS was detected; a single global index measured at delivery may not capture changes in specific antioxidant components [19]. The attenuation of the TOS difference after adjustment indicates that part of the signal may be shared with maternal age and BMI, which differed between groups and are associated with adverse outcomes in pregnancy [4] and with oxidative stress [20,21].

In contrast to the maternal compartment, no significant differences in cord TOS, TAS or OSI were detected between groups. Chelu et al. likewise reported no difference in cord blood

redox markers in GDM, although they used different assays (d-ROMs and BAP) [10]. The absence of a statistically significant difference does not establish equivalence, and this study was not designed to assess placental transfer. Maternal and cord TAS values were positively correlated with similar coefficients in both groups, whereas no significant correlation was detected for TOS. This pattern may reflect shared determinants of antioxidant capacity in the two circulations and compartment-specific generation or clearance of oxidants, but these mechanisms were not measured. Because the placenta is both a source and a target of oxidative stress [7], studies including placental tissue and specific markers are needed to address this question.

In the unadjusted comparison, cord ox-LDL was higher in the GDM group, but this difference did not remain significant after Holm correction. In the model adjusted for maternal age, BMI and parity, the group difference was smaller, and in the same model maternal BMI at delivery was associated with higher cord ox-LDL. No statistically significant correlation was detected between maternal and cord ox-LDL. When the GDM group was restricted to women recorded as diagnosed by the 100 g OGTT and the control group was retained, the group difference in cord ox-LDL was attenuated, whereas the association with maternal BMI was still observed.

Studies reporting an association between maternal obesity and oxidative stress in the fetoplacental unit [13,21] provide a biological context for this finding. However, BMI at delivery does not separate pre-pregnancy body weight from gestational weight gain, and the observational design does not allow us to determine whether the association reflects a direct effect or shared factors. Because cord ox-LDL has been associated with an indirect measure of insulin sensitivity in an earlier newborn cohort [14], this finding provides a rationale for examination in longitudinal studies.

Higher maternal triglycerides in GDM are part of the expected dyslipidemic pattern [22], but this difference was also attenuated after adjustment. No significant differences in cord lipid concentrations were detected between groups, in line with a previous study of cord blood lipoproteins [23], although equivalence cannot be inferred.

The strengths of this study include the assessment of paired maternal and cord samples obtained during the same delivery admission; the restriction to cesarean deliveries under regional anesthesia, which standardized the surgical and anesthetic conditions at delivery; and the use of complete-case non-parametric and adjusted analyses. Several limitations should be acknowledged. First, this was a single-center study with a moderate sample size and small treatment subgroups. Second, redox status was assessed with global assays (TAS, TOS and OSI); specific markers of oxidative damage and antioxidant defense, such as reduced glutathione, lipid peroxidation measured as TBARS, DNA oxidation and antioxidant enzyme activity, were not measured, and placental tissue was not examined. A recent systematic review and meta-analysis pooled data on malondialdehyde, 8-isoprostanes and superoxide dismutase, with high heterogeneity between studies, whereas total antioxidant and oxidant status were not pooled [11]; our findings therefore cannot be compared directly with pooled estimates. Third, about half of the maternal ox-LDL values and most cord Lp(a) values were at the highest and lowest reported values, respectively, which is compatible with censoring at the assay limits and limits the interpretation of these markers. In addition, maternal TOS values were higher than those reported in some previous studies, and the archived records do not document the measuring range of the analyzer application or whether a dilution correction was applied to high TOS results; the absolute values and between-group comparisons of TOS and OSI should therefore be interpreted with caution. Fourth, the groups differed in maternal age, BMI and parity; although we adjusted for these factors, residual confounding cannot be excluded, and BMI was measured at delivery rather than before pregnancy. Fifth, serum samples were stored at −80 °C until the laboratory

measurements of the original study, and the potential effects of storage on biomarker levels were not independently evaluated; measurements were made at a single time point. Sixth, the analyses were exploratory: many markers were compared without a pre-specified primary outcome, no group difference remained significant after Holm correction. Treatment subgroups were small and detailed data on glycemic control were not available; therefore, the independent effect of diet and insulin treatment on redox markers could not be separated from the glycemic differences that guided treatment selection. Larger studies with harmonized and more specific assays and pre-specified outcomes may be warranted.

5. Conclusions

In this exploratory study, maternal TOS and triglycerides were higher in women with GDM than in normoglycemic controls in unadjusted comparisons, whereas no significant differences in cord blood TAS, TOS or OSI were detected. Maternal and cord TAS values were correlated, whereas no significant correlation was detected for TOS. Cord ox-LDL was higher in GDM, and in the adjusted model it was associated with maternal BMI at delivery. The group differences were attenuated after adjustment and did not withstand correction for multiple comparisons. Because maternal diabetes has been associated with the long-term health of the offspring [24], future prospective studies could examine the associations of maternal glycemia and pre-pregnancy BMI with cord redox markers separately, add glutathione and lipid peroxidation measurements to the marker panel, and assess whether cord markers are related to metabolic outcomes in childhood.

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Abbreviations

BMI, body mass index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OGTT, oral glucose tolerance test; OSI, oxidative stress index; ox-LDL, oxidized low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status.

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