

Effect of Preeclampsia and Maternal Obesity on Neonatal Oxidative Stress Biomarkers and Endothelin-1 Levels

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Introduction

- Preeclampsia (PE):** Although less common in well-developed countries, PE remains one of the leading causes of maternal mortality worldwide, with an incidence between 3 and 10%. PE is responsible for 12-25% of fetal growth restriction and up to 20% of all preterm births.¹
- Obesity:** A major global health concern, obesity plays a role in adverse pregnancy conditions. Rates of gestational diabetes, hypertension, and stillbirths are greater in obese and overweight women, and their infants are at increased risk for neonatal complications. Obesity results in excessive adipocytes that contribute to maternal and neonatal oxidative stress.²
- Oxidative stress (OS):** Premature and critically ill infants are especially susceptible to OS as their intrinsic antioxidant system is immature and cannot fully compensate for the larger free radical load. OS is associated with severe neonatal illnesses (e.g., hypoxic ischemic encephalopathy, retinopathy of prematurity, and chronic lung disease (CLD)).³
- Endothelin-1 (ET-1):** A potent vasoconstrictor, ET-1 is associated with neonatal pathologies, including persistent pulmonary hypertension, CLD, and respiratory distress syndrome (RDS).⁴ ET-1 levels are elevated in preeclamptic women, and ET-1 is linked with hypertension in this condition.⁵ Both preeclampsia and obesity contribute to maternal and neonatal OS and related endothelial dysfunction in the ET-1 signaling pathway.

Objective

To determine the relationship between preeclampsia, maternal Body Mass Index (BMI) and neonatal levels of OS biomarkers [glutathione (GSH), malondialdehyde (MDA)] and ET-1.

Methods

Inclusion Criteria

- Gestational age (GA) at birth between 24 and 42 weeks; inborn status; Level IV NICU admission; written parental permission

Exclusion Criteria

- Congenital malformation incompatible with life

Study Population

- 63 neonates prospectively enrolled and divided into Preeclampsia and Non-Preeclampsia subgroups based on maternal diagnosis (Tab. 1) and Normal, Overweight and Obese subgroups based on maternal BMI (Tab. 2)

Specimen Collection

- Umbilical cord (u) and 24(±4) hours of life (24h) blood samples collected from indwelling catheter/heelstick for GSH, MDA and ET-1 analyses

Estimation of Plasma ET-1 Levels

- Plasma ET-1 analyses performed at Chicago College of Pharmacy, Midwestern University, USA, using a commercially available enzyme immunoassay kit (Enzo Life Sciences, NY)

Estimation of OS Marker Levels

Plasma levels of OS markers estimated using established methods:

- MDA: Ohkawa et al.⁶ (1979) (lipid peroxidation indicator)
- GSH: Ellman⁷ (1959)

Statistical Analyses

- One-way ANOVA for continuous; Fisher's exact test for categorical variables; P values <0.05 considered statistically significant

Table 1. Study Population Demographics (PE and Non-PE Subgroups)

| | Group 1: Preeclampsia (n = 11) | Group 2: Non-preeclampsia (n = 52) |
|------------------------------------|--------------------------------|------------------------------------|
| MATERNAL DATA | | |
| Age (yrs.) | 28.9 ± 7.26* | 30.27 ± 4.91* |
| Prenatal steroids (n) (%) | 6 (54.5%) | 20 (38.5%) |
| BMI | 35.08 ± 7.65* | 30.02 ± 6.18* |
| MODE OF DELIVERY (n) (%) | | |
| Vaginal Delivery | 5 (45.5%) | 22 (42.3%) |
| Caesarean Section | 6 (54.5%) | 30 (57.7%) |
| APGAR SCORES | | |
| 1 minute | 7.45 ± 1.75* | 7.12 ± 1.9* |
| 5 minutes | 8.63 ± 0.67* | 8.54 ± 1.0* |
| MATURITY (GA) (wks.) | | |
| Gestational Age | 32.2 ± 3.8* | 33.0 ± 4.10* |
| WEIGHT (g) | | |
| Birth weight | 1869.1 ± 964.4* | 1986.5 ± 746.6* |
| INTRAUTERINE GROWTH (n) (%) | | |
| Small for GA | 3 (27%) | 12 (23%) |
| Large for GA | 0 (0%) | 2 (7.7%) |
| GENDER (n) (%) | | |
| Female | 3 (27%) | 20 (28%) |
| Male | 8 (73%) | 32 (62%) |
| ETHNICITY (n) (%) | | |
| African American (non-Hispanic) | 0 (0%) | 4 (7.69%) |
| Asian | 0 (0%) | 6 (12%) |
| Caucasian | 4 (36%) | 36 (69.2%) |
| Hispanic | 7 (64%) | 6 (12%) |

*Mean ± SD

Table 2. Study Population Demographics (BMI Subgroups)

| | Normal BMI (18.5 – 24.9) (n = 9) | Overweight (25.0 – 29.9) (n = 26) | Obese (> 30) (n = 28) |
|---------------------------------|----------------------------------|-----------------------------------|-----------------------|
| MATERNAL DATA | | | |
| Age (yrs.) | 28.9 ± 5.43* | 31.1 ± 4.82* | 30.1 ± 6.16* |
| WEIGHT (g) | | | |
| Birth weight | 1194.8 ± 369.65* | 2175 ± 412.73* | 2971.5 ± 397.73* |
| MODE OF DELIVERY (n) (%) | | | |
| Vaginal delivery | 10 (41.7%) | 11 (42.3%) | 5 (38.5%) |
| Caesarean Section | 14 (58.3%) | 15 (57.7%) | 8 (61.5%) |
| APGAR SCORES | | | |
| 1-minute | 6.4 ± 2.08* | 7.8 ± 1.54* | 7.3 ± 1.55* |
| 5-minute | 8.2 ± 1.27* | 8.9 ± 0.33* | 8.6 ± 0.65* |
| MATURITY (GA) (wks.) | | | |
| Gestational Age | 28.8 ± 2.17* | 33.8 ± 1.28* | 38.4 ± 1.57* |
| GENDER (n) (%) | | | |
| Female | 9 (37.5%) | 11 (42.3%) | 3 (23.1%) |
| Male | 15 (62.5%) | 15 (57.7%) | 10 (76.9%) |
| Race/Ethnicity (n) (%) | | | |
| Asian | 1 (4.2%) | 3 (11.6%) | 3 (23.1%) |
| African American | 3 (12.5%) | 1 (3.8%) | 0 (%) |
| Caucasian | 13 (54.1%) | 18 (69.2%) | 9 (69.2%) |
| Hispanic | 7 (29.2%) | 4 (15.4%) | 1 (7.7%) |

*Mean ± SD

Results

Cord and 24h ET-1 Levels in PE and Non-PE groups

Mean uET-1 levels did not differ significantly between PE (8.42 ± 4.33 pg/mL) and non-PE (6.52 ± 3.66 pg/mL) subgroups (p>0.05). The mean 24h ET-1 level for the PE subgroup (6.36 ± 4.15 pg/mL) was significantly higher than the non-PE subgroup (4.31 ± 2.83 pg/mL) (p=0.049). (Fig. 1)

Cord and 24h MDA Levels in PE and Non-PE groups

No significant difference was found between mean uMDA levels in PE (3.10 ± 0.30 nmol/L) and non-PE (2.80 ± 0.61 nmol/L) subgroups (p>0.05). The mean 24h MDA level in the PE subgroup (1.40 ± 0.23 nmol/L) did not differ significantly compared with the non-PE (1.37 ± 0.42 nmol/L) subgroup (p>0.05).

Cord and 24h GSH Levels in PE and Non-PE groups

The mean uGSH level for the PE subgroup (0.84 ± 0.11 mmol/L) was significantly higher than the non-PE subgroup (0.71 ± 0.16 mmol/L) (P=0.03). (Fig. 2). No significant difference was found between the mean 24h GSH levels in the PE (0.65 ± 0.12 mmol/L) and non-PE (0.72 ± 0.15 mmol/L) subgroups (p>0.05).

Figure 1. Mean 24h ET-1 Levels in PE and Non-PE Subgroups

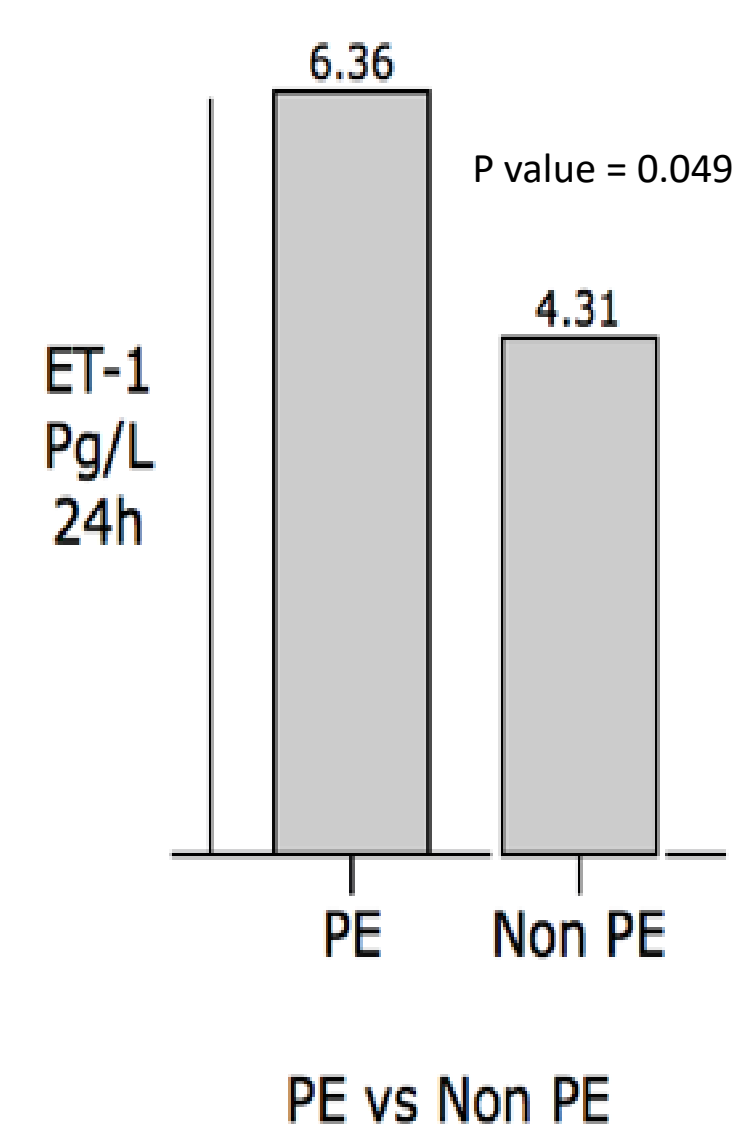
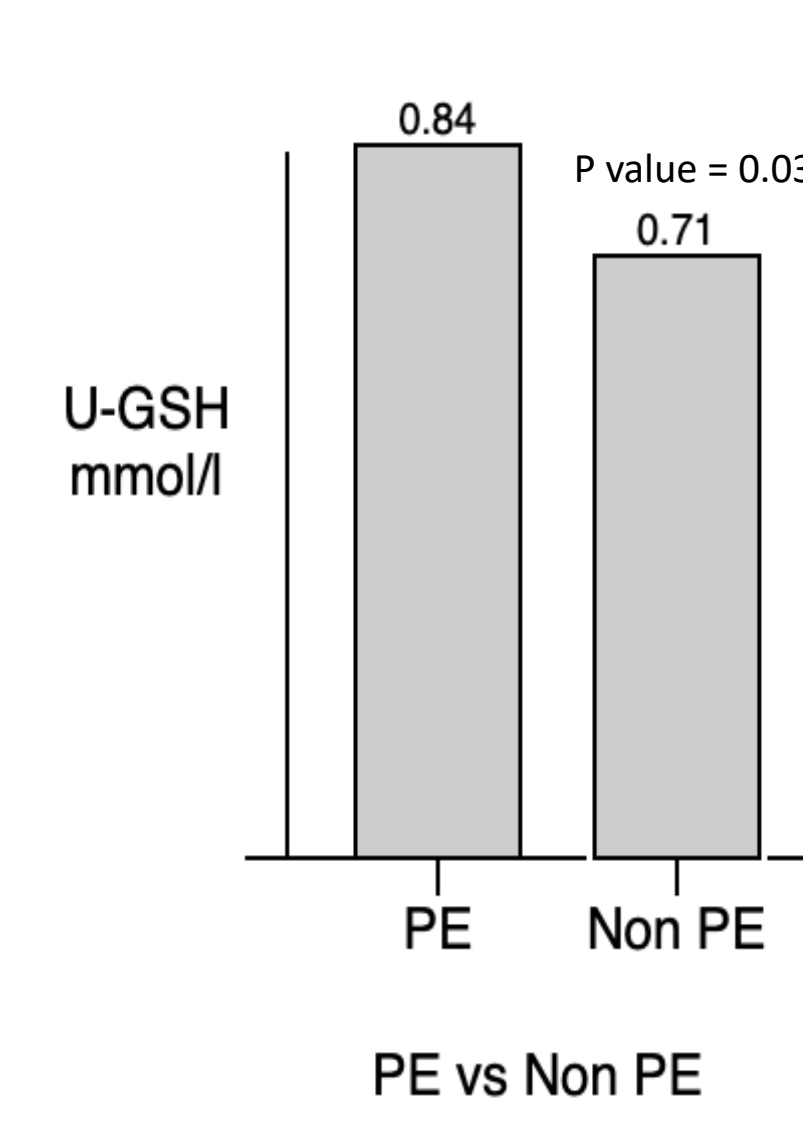


Figure 2. Mean uGSH Levels in PE and Non-PE Subgroups



OS Markers across Maternal BMI

Cord MDA and GSH levels did not correlate with BMI (r²=0.001, p>0.05 and r²=0.034, p>0.05, respectively), and no significant correlation was found between 24h MDA and GSH levels and BMI (r²=0.004, p>0.05 and r²=0.0001, p>0.05, respectively).

Umbilical Cord & 24h ET-1 Levels and Obesity

Mean plasma ET-1 levels in umbilical cord and 24h samples were significantly higher in neonates born to obese mothers (p<0.05). (Tab. 3)

Table 3. Umbilical Cord & 24h Plasma ET-1 Levels across BMI

| ET-1 Specimen Type | Normal BMI (n=9) | Overweight (n=26) | Obese (n=28) | P value |
|---------------------|----------------------------|----------------------------|----------------------------|---------|
| Cord (pg/mL) | 7.61 ± 1.74* (0.14-14.16)^ | 5.29 ± 0.61* (0.50-11.48)^ | 8.05 ± 0.67* (1.65-14.25)^ | p=0.021 |
| 24h of life (pg/mL) | 3.29 ± 0.62* (0.14-6.08)^ | 3.80 ± 0.46* (0.14-8.94)^ | 5.91 ± 0.70* (0.14-14.83)^ | p=0.015 |

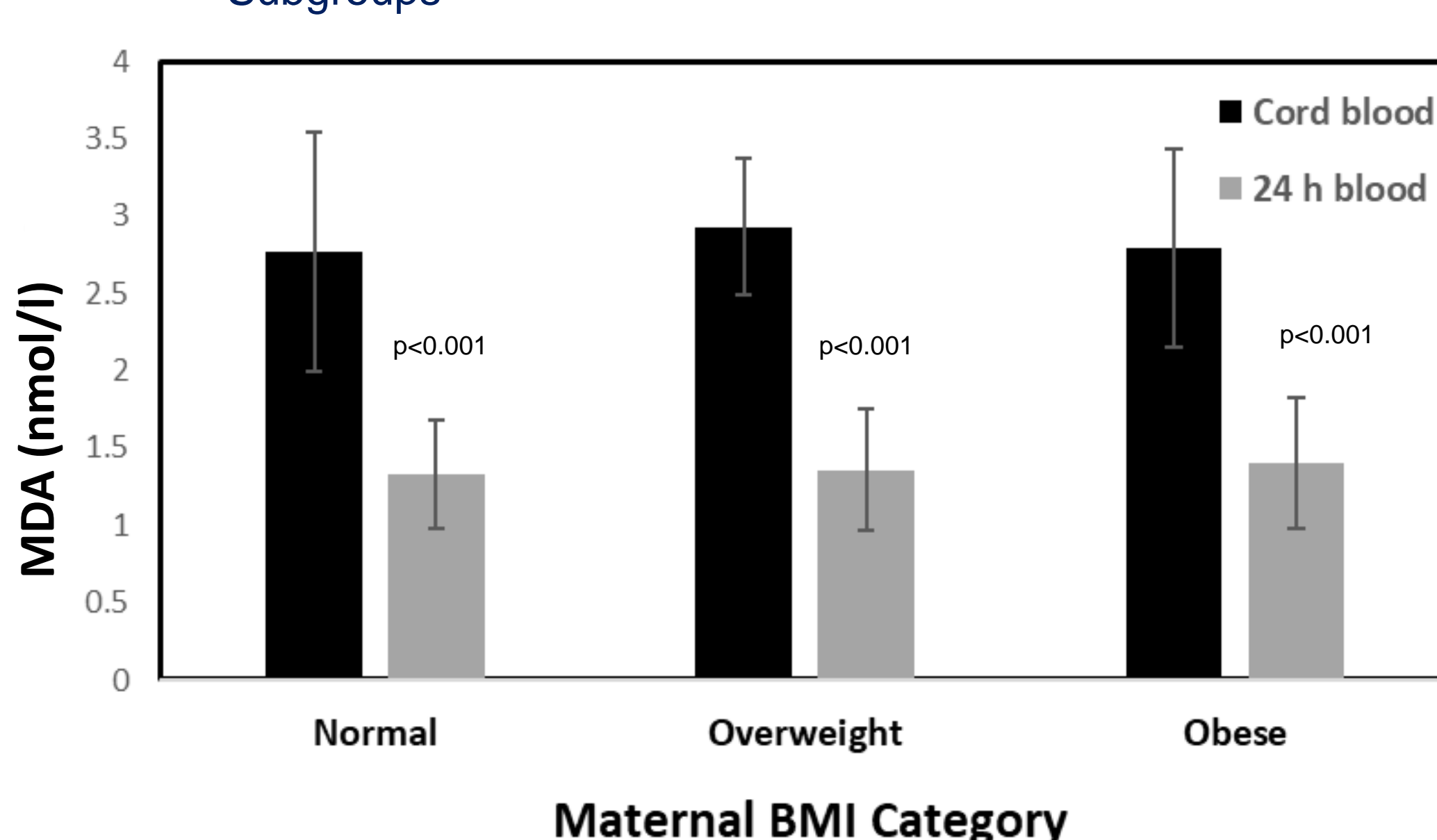
*Mean ± SEM, ^Range

Umbilical Cord and 24h OS Markers across BMI Groups

MDA: The mean cord blood level of all BMI subgroups: Normal (2.77 ± 0.08nmol/l), Overweight (2.93 ± 0.44nmol/l) and Obese (2.79 ± 0.64nmol/l) were significantly higher than those obtained at 24h of life (1.33±0.35nmol/l, 1.36 ± 0.39nmol/l, and 1.39 ± 0.43nmol/l, respectively; p<0.001). (Fig.3)

GSH: Mean plasma GSH levels did not differ significantly in either umbilical cord or 24h samples among the three BMI subgroups (p>0.05).

Figure 3. Umbilical Cord and 24h MDA Levels across Maternal BMI Subgroups



Umbilical Cord & 24h OS Markers

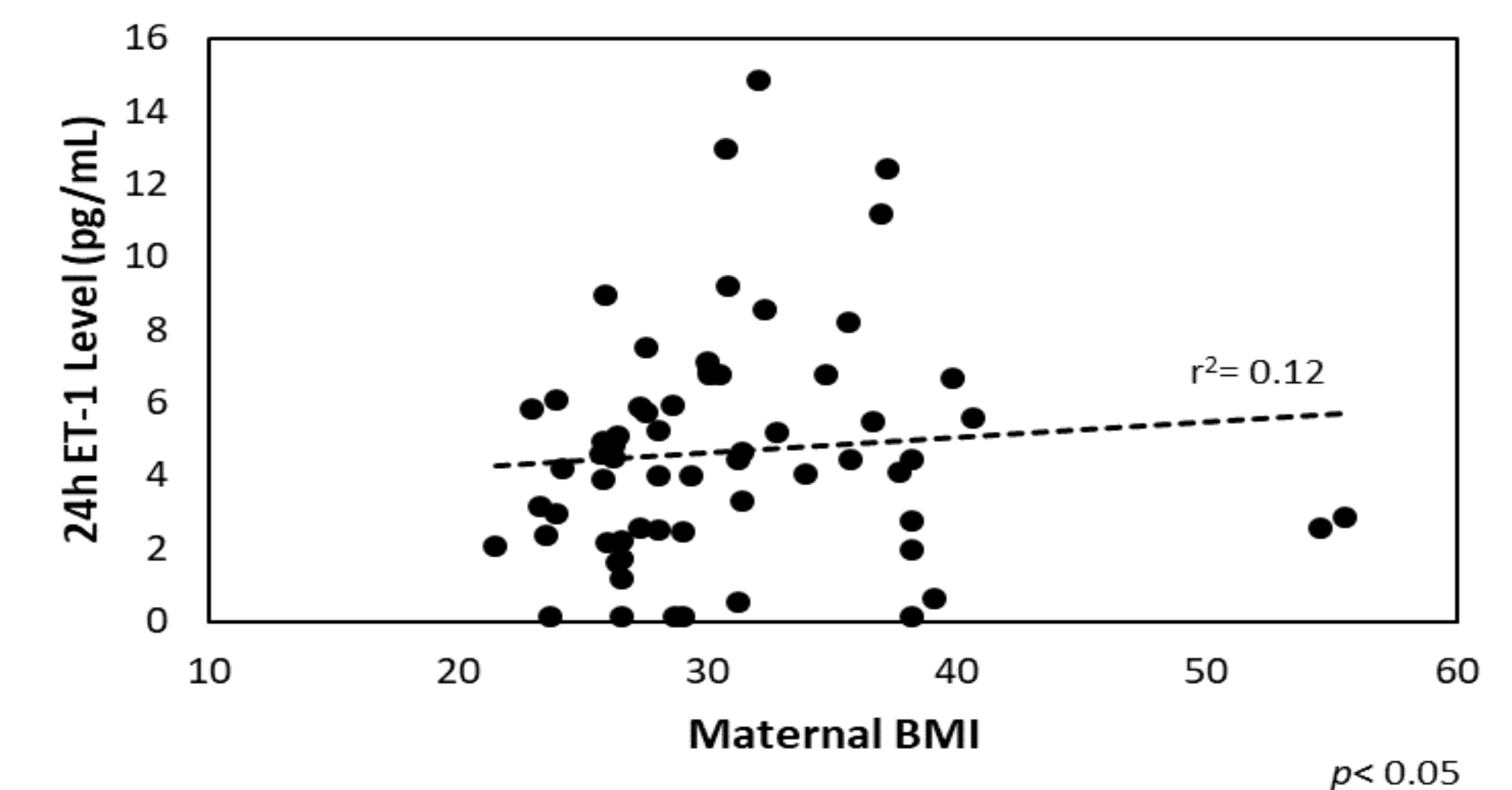
Only a weak negative correlation was found between MDA and GSH in cord blood (r²=0.025, p>0.05 and r²=0.0005, p>0.05) and 24h samples (r²=0.0007, p>0.05 and r²=0.032, p>0.05).

Results (cont'd)

Umbilical Cord & 24h ET-1 across Maternal BMI

Plasma ET-1 levels did not correlate significantly with BMI at birth (r²=0.03, p>0.05), but did correlate significantly at 24h of life (r²=0.12, p<0.05). (Figure 4)

Figure 4. Correlation between 24h ET-1 Levels & Maternal BMI



OS Markers and Oxygen Therapy

Mean MDA and GSH levels were significantly higher in neonates who received oxygen therapy at the time of delivery or thereafter in umbilical cord (p=0.005 and p<0.05, respectively) and 24h blood samples (p<0.005 and p<0.05, respectively) than those obtained from neonates who were not exposed to supplemental oxygen. (Tab. 4)

Table 4. OS Markers Levels Between Groups with/without O₂ Therapy

| OS Markers | Oxygen Therapy (n=23) | No Oxygen Therapy (n=40) | p Value |
|-----------------------------|-----------------------------|-----------------------------|---------|
| Umbilical Cord MDA (nmol/L) | 2.78 ± 0.14* (1.31 - 3.58)^ | 1.83 ± 0.23* (1.33 - 3.47)^ | 0.0049 |
| 24h MDA (nmol/L) | 1.42 ± 0.08* (0.89 - 1.67)^ | 0.84 ± 0.12* (0.59 - 2.20)^ | 0.0013 |
| Umbilical Cord GSH (mmol/L) | 0.62 ± 0.07* (0.49 - 0.94)^ | 0.36 ± 0.07* (0.47 - 1.19)^ | 0.0221 |
| 24h GSH (mmol/L) | 0.61 ± 0.08* (0.45 - 1.12)^ | 0.37 ± 0.06* (0.45 - 0.94)^ | 0.0227 |

*Mean ± SEM, ^Range

OS Markers & Prenatal Corticosteroids

Mean umbilical cord MDA levels in preterm neonates exposed to prenatal corticosteroids (1.87 ± 0.31nmol/l) were significantly lower (p<0.05) than those who were not exposed (2.85 ± 0.12nmol/l). No significant difference was found between these subgroups and 24h MDA or GSH (both cord and 24h levels) (p>0.05).

OS Markers and Mode of Delivery, Gender and Ethnicity

Mode of delivery and gender of neonates did not show a significant difference between OS marker levels in umbilical cord (p>0.05) or 24h blood samples (p>0.05). Similarly, no significant difference (p>0.05) was found between MDA and GSH levels based on race/ethnicity in samples drawn either at birth (u) or at 24h of life.

Conclusions

- Preeclampsia affects both OS and ET-1 levels in neonates and effects continue after delivery.
- Neonatal pro- and anti-OS markers (MDA and GSH) are independently affected by Preeclampsia and maternal BMI.
- Maternal BMI alone is not predictive of neonatal OS and related complications.
- Prenatal steroids may reduce OS injury directly via the lipid peroxidation pathway and/or indirectly by decreasing neonatal morbidities, such as RDS.
- Oxygen therapy increases levels of both oxidative stress markers (MDA and GSH) in neonates.

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