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ARGININE AND ADMA IN PREGNANT WOMEN WITH MAJOR DEPRESSION

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Abstract

Objective—Depression has been associated with vascular dysfunction, which may be of particular relevance in pregnancy. Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and L-arginine play a critical role in vascular function. The objective of this study was to investigate differences in ADMA, SDMA, and L-arginine among pregnant women with major depression compared to pregnant women without depression.

Methods—A case-control study was conducted in 21 depressed pregnant women and 42 matched controls. Maternal plasma ADMA, SDMA, and L-arginine were quantified, as well as C-reactive protein (CRP), urine excretion of ADMA, SDMA, L-arginine, and Arginase I.

Results—Plasma L-arginine and ADMA levels were significantly lower in the first trimester in women with depression (37.0 ± 9.2 and $0.298 \pm 0.06 \mu\text{mol/L}$, mean $\pm$ standard deviation [SD], respectively) compared to matched controls (42.1 ± 11.4 and $0.336 \pm 0.08 \mu\text{mol/L}$, $p=0.004$ and $p=0.002$ respectively) and across pregnancy ($p<0.001$ both). Depressed pregnant women had higher levels of plasma CRP (7.5 ± 3.7 vs. $5.1 \pm 4.0 \mu\text{g/mL}$, $p=0.027$), but no differences urine excretion of ADMA, SDMA, or L-arginine, or plasma levels of Arginase I (p values > 0.10).

Conclusions—Pregnant women with depression evidence lower plasma levels of L-arginine and ADMA. These differences are not explained by urinary excretion or Arginase I levels. The mechanism responsible for the observed differences in depressed pregnant women requires further research.

Keywords

pregnancy; depression; arginine; ADMA; SDMA; CRP

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INTRODUCTION

Depression is a major health issue, with a twelve month incidence around 8% and a lifetime prevalence of approximately 18%. (1) Women are nearly twice as likely to be affected by depression. (2) Although the neuropsychological consequences of depression have long been established, over the past decade studies have reported that depression is also linked to adverse physical health, including increased cardiovascular risk. (3) In addition, women who are depressed during pregnancy are at elevated risk of several adverse pregnancy outcomes including preterm birth, preeclampsia and postpartum depression. (4, 5) Depression is associated with a pro-inflammatory state, including elevated levels of C-reactive protein (CRP), Interleukin-6 and other inflammatory markers. (6) Patients with depression evidence impaired flow-mediated vasodilation, directly demonstrating impaired vascular function and a link to increased risk of future cardiovascular disease. (7) Together, these results suggest that vascular dysfunction may be an important underlying aspect of depression.

Asymmetric dimethylarginine (ADMA) is a novel and independent risk factor of cardiovascular disease (CVD) among low-, medium- and high-risk patient populations. (8) ADMA is an endogenous inhibitor of nitric oxide synthase (NOS), and metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). (9) ADMA is elevated in several disease conditions including obesity, diabetes, hypertension, hypercholesterolemia, and depression. (10-17) Elevated levels of ADMA and lower L-arginine are also associated with inflammatory states. (18) Consequently, it has been hypothesized that ADMA may be elevated in patients with depression. A study by Selley et al. found that ADMA was significantly elevated in individuals with major depression. (16) Their study investigated Australian men and women with a mean age of 46 years; however it is unclear whether this result is generalizable to other populations. Some studies have reported that L-arginine is lower in depression. (19) Experimental animal studies have reported improvements in depressive symptoms following both L-arginine supplementation and, paradoxically, administration of nitric oxide inhibitors. (20) In addition, experimental studies suggest micronutrient supplementation including the amino acid L-arginine may improve depressive and anxiety symptoms and improve birth outcomes in patients with perinatal depression. (21, 22)

Given the association between maternal depression and adverse pregnancy outcomes, and the link between depression and alterations in L-arginine and ADMA we hypothesized that ADMA would be elevated and L-arginine would be lower in pregnant women with major depression compared to non-depressed pregnant women. Therefore, the objective of this study was to investigate the relationship between maternal plasma concentrations of L-arginine and ADMA across pregnancy in relation to major depression among pregnant women.

MATERIALS AND METHODS

Participants

The study was conducted between February 2009 and June 2012 in a sample of 63 healthy nulliparous women with a singleton intrauterine pregnancy without known medical

complications recruited early in the first trimester (10.7 ± 3.1 weeks gestation, average $\pm$ SD). This was a nested case-control study from an ongoing longitudinal investigation of pregnancy (Prenatal Exposures and Preeclampsia Prevention (PEPP)) at the University of Pittsburgh, Magee-Womens Hospital and Magee-Womens Research Institute. Exclusion criteria included chronic hypertension, pre-gestational diabetes on medication (insulin, glyburide), major fetal anomaly or demise, planned termination of the pregnancy, collagen vascular disease (autoimmune disease) on medication, renal disease, epilepsy or other seizure disorder, active or chronic liver disease, heart disease, known illicit drug or alcohol abuse during current pregnancy. The study was approved by the University of Pittsburgh institutional review board. Participants were recruited to the study at the time of presentation to Magee-Womens Hospital for prenatal care. All pregnant women were informed about the study and gave written informed consent at study enrollment.

Assessments

All participants were enrolled early in the first trimester, 10.6 ± 3.1 weeks gestation for controls and 11.2 ± 2.9 weeks gestation for depression cases. Depressive symptoms were assessed using the Edinburgh Depression Scale (EDS), a previously validated scale for detection of depression during pregnancy (23), a 10-item screening tool providing an indication of the severity of symptoms. The PEPP study was designed such that the EDS was administered to all participants only at study enrollment. Women with EDS scores greater than or equal to 15 at the time of study enrollment were identified as major depression cases ($n=21$, average EDS score 17.8 ± 2.8); and this corresponded to the upper 5% of depression scores in this study population. Reliability of the EDS was found to be good with a Cronbach $\alpha = 0.86$. Participants with major depression were matched 2-to-1 by maternal age, race, pre-pregnancy body mass index (BMI), gestational age at delivery, and infant birth weight centile to non-depressed uncomplicated control pregnant women ($n=42$, average EDS score 4.2 ± 3.6).

Other assessments made at the time of study enrollment included the State-Trait Anxiety Inventory (STAI), the Life Orientation Test-Revised (LOT-R, an optimism/pessimism measure), and the Pittsburgh Sleep Quality Inventory (PSQI). Reliability of these measures was good with Cronbach α of 0.90, 0.87 and 0.89, respectively. Data from these questionnaires are presented in Table 1 to highlight differences between the cases of pregnant women with depression compared to non-depressed controls at study enrollment. In brief, the STAI is a self-report questionnaire consists of two subscales each containing 20 items, and measures anxiety at the moment of scoring. (24) The LOT-R is a validated instrument to determine individual differences in optimism/pessimism and has been shown to have high reliability among pregnant women. (25) The PSQI is an 18-item questionnaire used to assess habitual sleep quality over the previous month. Higher scores reflect poorer sleep quality and its psychometric properties have been validated in pregnant women. (26)

Blood samples

Maternal venous EDTA plasma samples were collected at study enrollment between 6-16 weeks gestation, the second trimester 16-26 weeks, third trimester 30-37 weeks, and at the time of admission for delivery. Samples were collected between February 2009 and June

2012 and stored at -70°C for later analysis. Power analysis based on previous published data indicated at least 10 participants with depression and 20 uncomplicated controls were needed to observe a 35% increase in ADMA with an alpha of 0.05 and 80% power.

ADMA, SDMA and L-Arginine quantitation

Maternal plasma and urine ADMA, SDMA and L-arginine concentrations were determined by high- pressure liquid chromatography (HPLC) as described by Teerlink et al. (27) In brief, samples were processed by solid phase extraction using Oasis MCX cation exchange SPE columns (30mg, 1 ml) (Waters, Milford, MA). N-monomethyl L-arginine (NMMA) was used as an internal standard; 50 μL of plasma from patients were spiked with 50 μL of 2 $\mu\text{mol/L}$ NMMA, and 900 μL of phosphate buffered saline, pH 7.4. Extracted plasma samples were injected onto a prepared HPLC system and the amino acids were derivatized online using a Waters 717 plus autosampler. Separation of the amino acids was performed using a Symmetry C18 column (3.9×150 mm, 5 μm particle size) with a Sentry Guard column (3.9×20 mm, 5 μm particle size). Standard curves were generated using known quantities of ADMA, SDMA, L-arginine, and NMMA spiked into buffer. All samples were measured in duplicate and the average was used for statistical analysis. The lower limit of detection is 0.01 $\mu\text{mol/L}$, with an inter-assay variability of $< 5\%$.

Standardization of Urine samples

Twenty-four hour urine excretion was determined by multiplying the HPLC ADMA, SDMA and L-arginine quantified values by a correction factor based on the creatinine concentration of the urine sample and the participant's estimated daily creatinine clearance. Urine creatinine concentration was determined by absorption spectrometry at 510 nm. Estimated daily clearance was determined based on age, race, gender, and lean body mass, as described by Ix et al. (28)

Arginase and C-reactive protein (CRP) quantitation

Maternal plasma Arginase type I was measured by ELISA (Cat. No. RD193028000R, Biovendor; Candler, NC). Sensitivity was 0.5 ng/ml. The intra- and inter-assay coefficients of variation were 4.9% and 10.5%. Maternal plasma CRP was measured by high-sensitivity ELISA as described previously. (29) The CRP standard curve is linear from 0.2 to 10ng/ml. Sensitivity was 0.2ng/ml and spike and recovery tests indicated 91 to 103% recovery. The intra- and inter-assay variability have been 3.9% and 6.5% respectively.

Exclusion of hemolyzed samples

Arginase levels can be significantly influenced by hemolysis in plasma samples, and therefore hemoglobin levels were also determined using the Harboe direct optical method, which was previously validated. (30) Samples with an adjusted hemoglobin score >20 were considered to be hemolyzed and thus excluded for Arginase I determination, resulting in 38 samples available for analysis (16 cases, 22 controls).

Statistical Analysis

Continuous data are presented as means and standard deviations (SD), and categorical data are expressed as numbers and percentages. Pregnant women with depression and non-depressed control women were matched 2-to-1 by maternal age, race, pre-pregnancy body mass index (BMI), gestational age at delivery, and infant birth weight centile and unpaired analyses were used to compare characteristics between groups (chi-square or t-test). Differences in maternal plasma concentrations of L-arginine, ADMA and SDMA between women with depression and non-depressed control women were assessed using the PROC MIXED procedure (with compound symmetry covariance structure) in SAS version 9.2 (SAS Institute, Cary, NC), which accounts for the correlation of observations within women and allows for randomly missing values. Random plasma samples collected from pregnant women with depression and non-depressed control women were missing at certain time points because of missed appointments or missing coverage at admission to labor and delivery. The values of L-arginine, ADMA, SDMA, and the L-arginine/ADMA ratio were normally distributed by the K-S Normality test. Tests were 2-sided and statistical significance was accepted at $p < 0.05$.

RESULTS

The study participant characteristics are shown in Table 1. By study design, participants identified as having major depression had significantly elevated EDS scores. Depressed participants also had significantly higher scores on the trait subscale of the State-Trait Anxiety Index (STAI) (31) and significantly lower scores on the Life Orientation Test – Revision (LOT-R, a validated measure of optimism) indicating increased anxiety and lower optimism among these women. (32) Depressed participants had worse sleep patterns, as measured by the Pittsburgh Sleep Quality Index, a validated (33) measure of sleep disturbances. Depressed participants were more likely to be current smokers (67% vs. 19%, $p < 0.001$), however a history of smoking was common in both cases and controls (81% vs. 61%, $p = 0.13$). There was no difference in alcohol use or household income between cases and controls.

Association of depression with C-reactive protein

As shown in Table 1, pregnant women with depression evidenced increased inflammation as maternal plasma levels of CRP in the first trimester were significantly elevated in women with depression compared to non-depressed controls (7.5 ± 3.7 $\mu\text{g/mL}$ vs. 5.1 ± 4.0 $\mu\text{g/mL}$, $p = 0.027$) as reported previously. (6) Elevated CRP was not associated with maternal smoking or alcohol use (CRP smokers vs. non-smokers; and CRP alcohol use vs. no alcohol use).

Plasma L-Arginine and ADMA levels across pregnancy in women with depression

As shown in Figure 1, maternal plasma levels of L-arginine were significantly different across pregnancy ($F_{3,59} = 45.01$, $p < 0.001$) as previously reported. (17) Consistent with our initial hypothesis, maternal plasma L-arginine levels were significantly lower across pregnancy among pregnant women with depression compared to non-depressed pregnant women ($F_{1,61} = 8.36$, $p = 0.007$). However, there was no significant interaction between

depression status and time indicating that the rate of change across pregnancy was similar for depressed vs. non-depressed women ($F_{3,59}=0.49$, $p=0.69$). As shown in Figure 2, contrary to our original hypothesis maternal plasma levels of ADMA were also significantly lower among pregnant women with depression compared to non-depressed control women ($F_{1,61}=10.43$, $p=0.002$). As expected, maternal plasma levels of ADMA were significantly different across pregnancy ($F_{3,59}=8.24$, $p<0.001$), however there was no significant interaction between depression status and time indicating that the rate of change of ADMA across pregnancy was similar for depressed vs. non-depressed women ($F_{3,59}=0.46$, $p=0.71$). As shown in Figure 3, maternal plasma SDMA levels were significantly different across pregnancy ($F_{3,59}=24.18$, $p<0.001$). However, SDMA levels were not different between pregnant women with depression compared to non-depressed pregnant women ($F_{1,61}=1.03$, $p=0.32$); and there was no significant interaction between depression status and time indicating that the rate of change for SDMA was similar for depressed vs. non-depressed women ($F_{3,59}=0.78$, $p=0.51$). Given the overall lower levels of L-arginine, ADMA and SDMA among pregnant women with depression the L-arginine/ADMA and ADMA/SDMA ratios (Table 2) were not different between pregnant women with major depression compared to non-depressed controls.

Excretion of ADMA, L-Arginine, and SDMA in women with depression

We next investigated if the lower levels of plasma L-arginine and ADMA in pregnant women with depression was the result of increased urinary excretion. As shown in Table 3, there was no significant difference in urinary excretion of L-arginine, ADMA, or SDMA between depressed and non-depressed pregnant women in the first trimester.

Arginase I levels in pregnant women with and without depression

We next investigated if there was a difference in Arginase I levels between pregnant women with depression compared to controls. There was no significant difference in Arginase I levels between pregnant women with depression compared to controls at the time of study enrollment (27.8 ± 24.0 vs. 31.0 ± 21.5 ng/ml respectively, $p=0.66$). Of note, Arginase I levels at study enrollment were also not significantly different between depressed cases and controls when all samples were analyzed adjusting for hemoglobin levels (28.8 ± 22.1 vs. 37.7 ± 27.1 ng/ml respectively, $p=0.19$).

DISCUSSION

The present study represents the first to quantify maternal plasma ADMA and L-arginine levels longitudinally during pregnancy in women with depression. Our results show that pregnant women with depression evidence a relative deficiency of circulating L-arginine compared to non-depressed healthy controls. We observed a relative decrease in L-arginine levels of approximately 10% among pregnant women with depression and this difference was significant across pregnancy. This is consistent with the current literature, which suggests that circulating L-arginine levels are lower in patients with depression. (19) Our results may indicate that arginine supplementation, either directly or in the form of citrulline which is readily converted to arginine, may be of potential benefit to women with depressive symptoms, given their lower levels of L-arginine across pregnancy. However, the Edinburgh

Depression Scale (like most metrics commonly used to screen for depression) does not reflect total duration of depressive symptoms; L-arginine levels may be significantly lower in patients who have experienced chronic depression compared with those whose symptoms are of recent onset.

Our results showed increased levels of inflammation as evidenced by elevated CRP in depressed participants, consistent with previous literature. (6) Contrary to our original hypothesis this increased inflammation was not associated with elevated levels of ADMA in depressed pregnant patients. In contrast, we report finding significantly lower maternal ADMA levels among pregnant women with depression. Given that depressed participants were more likely to be cigarette smokers and smoking has been associated with increased ADMA levels (34), the actual reduction in ADMA levels associated with depression may be greater than reflected in our data. These results contrast with the only other study linking depression and ADMA, which reported an increase in ADMA levels among participants with depression. (16) However, the participants in that study represented a different population compared to our study, as it included men and non-pregnant women with a mean age of 47 years while our study consisted solely of young reproductive age pregnant women. It is well established that ADMA levels are significantly different in pregnancy compared to a non-gravid state. (35) However, our current study as well as several in the literature have associated depression with increased inflammation (3, 6), and increased inflammation has in turn been correlated with elevated ADMA. (18) Our results suggest increased inflammation may not necessarily lead to elevated levels of ADMA during pregnancy.

In order to try and determine the underlying cause of lower maternal plasma L-arginine and ADMA levels among pregnant women with depression, we evaluated both urinary excretion as well as catabolism by serum Arginase. Although previous studies have shown that Arginase activity is elevated in depression (36), we did not find a difference in levels of circulating Arginase I between depressed and non-depressed pregnant women at study enrollment. However, the previous study differs from ours in several ways. In addition to investigating non-pregnant participants, the study by Elgun et al. also evaluated Arginase activity via the breakdown of arginine into ornithine. This difference in activity does not distinguish between Arginase I and II which our assay is unable to detect. Elevated endothelial Arginase II in umbilical vessels has been associated with vascular dysfunction and intrauterine growth restriction (IUGR) during pregnancy; although we found no studies investigating serum Arginase II in depression or pregnancy, endothelial Arginase II may contribute to the decrease in plasma L-arginine that we observed among pregnant women with depression. Although we did not exclude dietary differences as a possible source of differences in arginine levels, previous data indicates that even complete exclusion of arginine from the diet would not account for the differences in arginine we observe in our study. (37) Therefore it is unlikely that normal variations in diet are sufficient to explain our results. In addition, the lack of differences in the L-arginine/ADMA and ADMA/SDMA ratios likely indicates the lower levels of L-arginine and ADMA in the pregnant women with depression is likely not the result of increased ADMA metabolism by DDAH, differences in ADMA production (which would affect the ADMA/SDMA ratio since these are produced in parallel) or differences in renal clearance since SDMA is cleared only by the kidney in contrast to ADMA which is primarily metabolized by DDAH. Therefore, it is more likely

that our data may be the result of alterations in whole body production of L-arginine and ADMA by protein arginine methyltransferases, such as that found in disorders of urea cycle enzymes. (38) Further investigation is required to determine the specific mechanisms by which L-arginine and ADMA levels are preferentially lower in pregnant women with depression.

To our knowledge, this study is the first to investigate L-arginine, ADMA and SDMA levels across pregnancy among depressed pregnant women. This is an important population to consider, as it is established that levels of ADMA and L-arginine during pregnancy are significantly different than levels outside of pregnancy (35, 39), and that abnormal levels of ADMA and L-arginine during pregnancy are associated with pregnancy complications such as preeclampsia. (17, 39) In addition, women who are depressed during pregnancy are at increased risk of several adverse pregnancy outcomes including preterm birth, preeclampsia and postpartum depression. (4, 5) Additional strengths of this study include its longitudinal nature, which allowed us to investigate the change in plasma levels of ADMA and L-arginine over the course of pregnancy, rather than simply looking at a cross section of women at different gestational ages. We also controlled for several factors, including race and body mass index, which have been reported to be associated with altered ADMA/L-arginine levels. We also controlled for gestational age and birth weight centile, which may have diminished the differences we were able to detect between cases and controls. At the same time, this ensures the observed differences are the result of depression rather than other factors that may be affecting intrauterine growth or time of gestation. Limitations of this study include the relatively small sample size and the absence of samples at all investigated time points, particularly at delivery. However, this is not an unexpected complication of longitudinal studies of pregnant women. In addition, although the Edinburgh Depression Scale is well validated as a screening tool for depression during pregnancy (23), it does not allow us to determine a woman's history of depressive symptoms. It is likely that the duration and intensity of depressive symptoms prior to conception are relevant to the extent of physiologic dysfunction (such as altered ADMA and L-arginine) observed throughout pregnancy. Finally, our participant groups differed in smoking status; as described above, however the majority of participants in both groups are identified as smokers and differences in smoking status would be expected to be associated with elevated ADMA levels.

Future research should confirm our data in larger samples of patients, particularly those with a longstanding history of depression. As noted above, it may be useful to measure Arginase activity and/or endothelial Arginase (I, II, or both) levels in this population. In addition, it would be worthwhile to investigate whether L-citrulline supplementation is able to restore normal plasma L-arginine levels in women with depression, and whether this benefits depressive symptoms. Presently, our data suggest that depression during pregnancy is associated with lower maternal L-arginine, a necessary precursor to the synthesis of nitric oxide, which plays a key role in vascular function. We also find a significant decrease in ADMA levels in depressed women compared with healthy pregnant controls, which does not appear to be the result of either increased excretion or increased catabolism by Arginase I. In light of the high prevalence of depression, which is often undiagnosed (1), this area of research has significant implications for a large number of pregnant women, both in

assessing a woman's risk for adverse events during pregnancy and potentially reducing this risk through treatment of the underlying metabolic disturbances.

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Glossary

ADMA	asymmetric dimethylarginine
SDMA	symmetric dimethylarginine
CRP	C-reactive protein
CVD	cardiovascular disease
NOS	nitric oxide synthase
DDAH	dimethylarginine dimethylaminohydrolase
PEPP	Prenatal Exposures and Preeclampsia Prevention
EDS	Edinburgh Depression Scale
BMI	body mass index
STAI	State-Trait Anxiety Inventory
LOT-R	Life Orientation Test–Revised
PSQI	Pittsburgh Sleep Quality Inventory
HPLC	high-pressure liquid chromatography
NMMA	N-mono-methyl L-arginine
IUGR	intrauterine growth restriction
ANOVA	analysis of variance
SD	standard deviation

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Figure 1.

Maternal plasma L-arginine is lower across pregnancy in women with depression compared to non-depressed control pregnant women, $p=0.007$. L-arginine is significantly different across pregnancy, $p<0.001$. Data are mean $\pm$ SE. Circle and solid line represent control patients. Triangle and dashed line represent pregnant women with depression.

Figure 2.

Maternal plasma ADMA is lower across pregnancy in women with depression compared to non-depressed control pregnant women, $p=0.002$. ADMA is significantly different across pregnancy, $p<0.001$. Data are mean $\pm$ SE. Circle and solid line represent control patients. Triangle and dashed line represent pregnant women with depression.

Figure 3.

Maternal plasma SDMA is not significantly lower in women with depression compared to non-depressed control pregnant women, $p=0.32$. SDMA is significantly different across pregnancy, $p<0.001$. Data are mean $\pm$ SE. Circle and solid line represent control patients. Triangle and dashed line represent pregnant women with depression.

Table 1**Maternal and Newborn Characteristics of Study Participants**

	Major depression participants (n=21)	Non-depressed control participants (n=42)
Maternal age (years)	22.5 ± 4.4	21.7 ± 3.7
Pre-pregnancy body mass index (BMI) (kg/m ²)	30.6 ± 7.8	30.6 ± 7.7
Race (African American) n (%)	15 (71.4%)	30 (71.4%)
Average blood pressure at enrollment (mmHg)	106 ± 10/69 ± 7	109 ± 9/71 ± 7
Gestational age at delivery (weeks)	38.4 ± 3.3	38.1 ± 3.5
Infant birth weight (grams)	3231 ± 743	3055 ± 681
Infant birth weight centile (%)	56 ± 30	50 ± 25
Edinburgh Depression Scale (EDS) score at study enrollment	17.8 ± 2.8 *	4.2 ± 3.6
Trait subscale of State-Trait Anxiety Index (STAI) at study enrollment	25.3 ± 4.8 *	15.8 ± 3.2
Life Orientation Test -Revision (LOT-R) at study enrollment	12.0 ± 4.2 *	15.2 ± 3.0
Pittsburgh Sleep Quality Inventory	26.1 ± 4.5 *	19.7 ± 5.1
Household Income •		
<\$10,000	7/18 (39%)	12/26 (46%)
\$10-34,999	8/18 (44%)	9/26 (35%)
\$35,000+	3/18 (17%)	5/26 (12%)
History of Alcohol Use	81%	71%
Lifetime History of Smoking	81%	61%
Smoking during Pregnancy	67% *	19%
Average cigarettes/day prior to pregnancy	10.8 ± 9.9	5.1 ± 6.7
Plasma C-reactive protein (µg/mL)	7.5 ± 3.7 [#]	5.1 ± 4.0

Data are mean ± SD.

* p<0.010 compared to non-depressed control participants.

[#] p<0.050 compared to non-depressed control participants.

• 3 cases and 16 controls listed their income as "unknown" and were excluded from this analysis; difference not significant by Fisher exact test (p=0.850).

Table 2

Differences in maternal L-Arginine, ADMA and SDMA by trimester

		First Trimester	Second Trimester	Third Trimester	Delivery
Gestational age at sample collection in weeks (n)	Depressed	11.2±2.9 (21)	20.3±2.4 (16)	35.4±1.0 (17)	39.3±1.3 (14)
	Controls	10.6±3.1 (42)	20.3±1.8 (41)	34.7±2.5 (37)	38.4±4.1 (28)
Plasma L-arginine/ ADMA ratio	Depressed	126±34	127±40	96±38	74±22
	Controls	130±43	125±39	99±25	76±19
Plasma ADMA/ SDMA ratio	Depressed	0.95±0.20	0.92±0.17	0.90±0.20	0.90±0.19
	Controls	0.99±0.24	0.96±0.26	0.89±0.22	0.90±0.32

Data are mean ± SD.

Table 3

First Trimester urine excretion of ADMA, L-Arginine, and SDMA

	ADMA (μmol/24hr)	L-Arginine (μmol/24hr)	SDMA (μmol/24hr)
Depressed participants	42.4±9.9	204.3±52.6	39.2±13.2
Non-depressed control participants	41.2±12.5	192.9±76.0	41.4±14.8

Data are mean ± SD.