

Maternal and cord steroid sex hormones, angiogenic factors, and insulin-like growth factor axis in African-American preeclamptic and uncomplicated pregnancies

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Abstract

Background A history of a preeclamptic pregnancy has been associated with subsequent increased risk of cardiovascular disease in the mother and decreased risk of breast cancer in both the mother and offspring. The concentrations of steroid sex hormones, angiogenic factors, and other proteins during pregnancy are important components of the in utero environment and may mediate the association of preeclampsia with later health outcomes. This study sought to compare an extensive profile of biological markers in both maternal and umbilical cord samples in preeclamptic and uncomplicated pregnancies of a predominantly African-American population.

Methods Steroid sex hormones, angiogenic factors, and components of the insulin-like growth factor axis were measured in maternal and umbilical cord sera from 48 pregnancies complicated by preeclampsia and 43 uncomplicated pregnancies. Regression models estimated the

associations of these markers with preeclampsia, after adjusting for maternal and gestational age.

Results Concentrations of androgens (testosterone $p = 0.06$ and androstenedione $p = 0.08$) and the anti-angiogenic factors soluble fms-like kinase 1 ($p = 0.004$) and soluble endoglin ($p = 0.004$) were higher in the maternal circulation of women diagnosed with preeclampsia. These findings also were noted when the analyses were restricted to only African-American participants (77% of overall study population). Furthermore, among African-Americans, cord insulin-like growth factor-1 was lower in preeclamptic pregnancies than in controls.

Conclusions The associations of maternal androgens and anti-angiogenic factors with preeclampsia are consistent with prior reports from predominantly Caucasian populations. Alterations in these analytes as well as other maternal and fetal biomarkers in preeclampsia could mediate the associations of preeclampsia with later health consequences.

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Keywords Preeclampsia · African-American · sFlt-1 · IGF · Leptin · Prolactin

Introduction

A diagnosis of preeclampsia during pregnancy has been associated with a subsequently increased risk of cardiovascular disease in the mother [1–3] as well as in the offspring [1, 4, 5]. Conversely, a history of preeclampsia has been related to a reduced risk of breast cancer for the mother, and limited data suggest that this protection extends to the offspring [6, 7]. Variations in steroid sex hormones and angiogenic factors have been associated with both preeclampsia [8, 9] and these later health outcomes [7, 10–14] and may be involved in the underlying biological mechanisms that lead to altered disease risks.

Preeclampsia is defined by the onset of hypertension and proteinuria after 20 weeks of pregnancy and occurs in approximately 5–7% of pregnant women in the United States [15]. Angiogenesis, the process of new blood vessel formation from preexisting vessels, and vascular remodeling are critical in placental establishment and functioning. The process of angiogenesis during placentation is tightly regulated by both pro- and anti-angiogenic factors. In pregnancy complications such as preeclampsia, circulating maternal angiogenic factors are disturbed, and normal uteroplacental vessel remodeling is greatly reduced [16].

Previous studies in predominantly Caucasian women have shown that women who develop preeclampsia have highly elevated circulating levels of the anti-angiogenic proteins soluble fms-like kinase 1 (sFlt1) and soluble endoglin (sEng), both prior to and at clinical diagnosis of the disease [17–25]. African-American women have higher rates of preeclampsia and higher prevalence of preeclampsia risk factors (e.g., elevated BMI) than Caucasians [26–29]. Androgens (testosterone and androstenedione) have also been shown to be higher in maternal circulation in healthy pregnant African-American women compared to Caucasian women [30], while among Caucasian women, these same androgens were increased in women with preeclampsia [8, 31, 32]. Here, we sought to explore the associations of preeclampsia with several steroid sex hormones and angiogenic factors, in addition to other less-studied analytes including components of the insulin-like growth factor (IGF) axis and prolactin in a case–control study conducted in a primarily African-American population to determine whether these associations are similar to those found in largely Caucasian populations.

Methods

Study design and population

Participants included in the present analysis were from a case–control study of preeclampsia conducted at Louisiana State University Health Sciences Center at Shreveport, LA, from 2003 to 2006 [33]. Preeclampsia (cases) was diagnosed as blood pressure $\geq 140/90$ mmHg on two separate readings at least 6 h apart and urine protein measurement of 1+ or more on urine test strip or 24 h urine protein collection ≥ 300 mg in the specimen. Women with uncomplicated pregnancies (controls) were defined as pregnancy with normal blood pressure ($< 140/90$ mmHg), without proteinuria and matched to cases on maternal age. Cases and controls were required to have singleton pregnancies that were normotensive before 20 weeks gestation and were excluded from the study if they had chronic hypertension, preexisting or gestational diabetes mellitus, chronic renal disease, or conceptions through any fertility treatment. Initially, only nulliparous women were recruited, but this criterion was relaxed later in the study. The original study was approved by the Institutional Review Boards (IRB) of Louisiana State University Health Sciences Center and The Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Data collection and laboratory assays

Medical and demographic information for both mother and offspring was obtained from an in-person interview and medical chart review. Maternal blood samples were collected after consent was obtained when patients were admitted to the labor unit at LSUHSC-S hospital and cord blood was sampled at delivery and processed as described previously [33]. Estradiol (E2), estriol (E3), androstenedione (A4), testosterone (T), progesterone (P), prolactin (PRL), soluble fms-like kinase 1 (sFlt-1), soluble endoglin (sEng), placenta-like growth factor (PLGF), insulin-like growth factor 1 (IGF-1), insulin-like growth factor 2 (IGF-2), insulin-like growth factor-binding protein 3 (IGFBP-3), C peptide and leptin were assayed in maternal and cord sera. Details of the laboratory assays for all measurements in this population have been published previously (Faupel-Badger, et al., in press). Coefficients of variation (CVs) based on blinded duplicates were less than 10% for all analytes except for maternal A4, E3, and P, which were all $< 15\%$, and maternal sEng that was 29%. For cord measures, all analytes had CVs $< 10\%$ except cord A4 and T ($< 15\%$) and E2 (16.3%). Because of limited sera, cord measurements were prioritized based on assay volume requirements to achieve the maximum results from each

sample; thus, the sample sizes vary among some of the analytes.

Statistics

t tests were conducted to evaluate statistical differences in maternal and neonatal characteristics by case status and to determine variables for inclusion in multivariate analysis of protein and hormone measures. The protein and hormone measures were transformed to the natural logarithm values. Linear regression models using continuous values of the proteins and hormones as the dependent variable estimated the associations with preeclampsia after adjustment for variable significantly different between preeclamptic and normal pregnancies (i.e., maternal and gestational age). Birth weight, length, and head circumference were not included in the model as these variables are highly correlated with gestational age ($r_s = 0.5\text{--}0.8$). Analyses were performed using SAS (version 9.0, SAS Institute, Inc., Cary, NC), and statistical significance was defined as two-sided $p < 0.05$.

Results

Demographics of study population

The maternal, gestational, and neonatal characteristics of the study population are reported in Table 1. A total of 91 women (43 cases and 48 controls) participated in this study, including 34 cases and 44 controls who were nulliparous. In addition, 62.8% ($n = 27$) of preeclamptic pregnancies and 77.1% ($n = 37$) of controls were African-American; the remainder were Caucasian (15 preeclamptic and eight normal pregnancies) and Hispanic (one preeclamptic and three normal pregnancies). As expected, offspring from preeclamptic pregnancies were delivered

earlier and weighed less than offspring from normal pregnancies. Mothers with preeclampsia were more likely to have delivered by Cesarean section (65% vs. 35%, $p = 0.005$) than mothers with normal pregnancies. There were no significant differences in maternal height, pre-pregnancy weight or body mass index (BMI), and pregnancy weight gain or offspring gender between the two study groups, although BMI and pregnancy weight gain were 11 and 16% higher in the cases. Fewer women had cord samples than had maternal samples. Table 1 presents the results for the larger population with maternal samples, however, when these analyses were restricted to only those women with both maternal and cord samples, the medians and significance of the results remained largely unchanged.

Associations of analytes with preeclampsia

Means for the sex steroids and proteins measured in maternal and cord samples are presented in Table 2 adjusted for maternal age and gestational age. Maternal concentrations of the anti-angiogenic proteins sFlt-1 and sEng were significantly higher in women with pregnancies complicated by preeclampsia. Maternal T and A4 were also higher (42 and 33% higher, respectively) in preeclamptic pregnancies, but these differences did not reach statistical significance. There were no statistically significant differences in maternal estrogens, IGF axis, P or PRL between groups. Cord concentrations of E3, IGF-1, and C peptide were lower in preeclamptic pregnancies, but overall there were no significant differences in cord analyte concentrations between preeclamptic pregnancies and controls. Including maternal BMI, offspring gender, or mode of delivery in the linear regression model examining association of maternal or cord analytes with case-control status did not substantially alter the results from those obtained after adjusting only for gestational age and maternal age (results not shown).

Table 1 Median values for maternal and neonatal characteristics

	Cases		Controls		p^a
	<i>n</i>	Median (range)	<i>n</i>	Median (range)	
Gestational age	43	34.0 (24.0–42.0)	48	39.0 (34.0–41.3)	<0.0001
Birth weight (grams)	43	1,742 (410–3,290)	48	3,206 (2,385–4,110)	<0.0001
Birth length (cm)	43	41.8 (26.0–51.0)	47	48.0 (20.0–54.6)	0.0008
Head circumference (cm)	43	31.0 (20.5–35.5)	47	34.0 (30.5–37.0)	<0.0001
Maternal age (years)	43	21 (16–38)	45	20 (15–32)	0.04
Maternal height (in)	43	63 (59–71)	48	64 (59–70)	0.57
Pre-pregnancy maternal weight (lbs)	40	144 (95–350)	45	140 (95–250)	0.21
Maternal weight gain (lbs)	35	37 (4–98)	45	32 (–18–114)	0.12
Pre-pregnancy maternal body mass index (kg/m ²)	40	26.5 (18.0–54.8)	45	23.8 (16.8–43.1)	0.16

^a *p* value from *t* test

Table 2 Geometric means of analytes adjusted for gestational age and maternal age

	Cases			Controls		95% CI	<i>p</i> value
	<i>n</i>	Adjusted mean	95% CI	<i>n</i>	Adjusted mean		
A4 (ng/ml)							
Maternal	43	6.39	5.18, 7.88	48	4.80	3.94, 5.83	0.08
Cord	28	6.91	5.41, 8.83	34	8.22	6.63, 10.21	0.35
Testosterone (ng/ml)							
Maternal	43	300	237, 381	48	211	169, 264	0.06
Cord	28	42.6	26.7, 67.9	34	39.8	26.4, 60.1	0.85
Estradiol (ng/ml)							
Maternal	43	15.3	9.1, 25.6	48	10.0	6.2, 16.2	0.29
Cord	28	17.1	10.7, 27.2	34	16.9	11.2, 25.5	0.98
Estriol (ng/ml)							
Maternal	41	9.11	6.05, 13.73	48	7.29	5.04, 10.56	0.48
Cord	25	80	35, 182	29	252	120, 532	0.07
Progesterone (ng/ml)							
Maternal	42	140	105, 188	48	102	78, 134	0.16
Cord	28	1,067	720, 1,581	31	1,704	1,187, 2,445	0.13
Prolactin (ng/ml)							
Maternal	43	143	119, 171	48	139	118, 165	0.87
Cord	28	310	230, 420	34	251	192, 327	0.35
IGF1 (ng/ml)							
Maternal	42	147	115, 187	47	136	108, 170	0.68
Cord	21	51	38, 68	28	77	60, 98	0.06
IGF2 (ng/ml)							
Maternal	41	1,767	1,583, 1,972	48	1,770	1,603, 1,955	0.99
Cord	22	710	586, 861	25	711	595, 849	0.82
IGFBP3 (ug/ml)							
Maternal	43	4.87	4.37, 5.42	48	5.08	4.59, 5.61	0.61
Cord	27	1.30	1.05, 1.62	34	1.45	1.20, 1.75	0.51
C peptide (ng/ml)							
Maternal	29	0.72	0.54, 0.96	35	0.70	0.54, 0.91	0.92
Cord	11	0.37	0.27, 0.51	12	0.57	0.42, 0.77	0.10
Leptin (ng/ml)							
Maternal	41	38.3	29.7, 49.4	46	28.4	22.4, 36.0	0.13
Cord	17	6.2	3.3, 11.4	22	12.5	7.4, 21.0	0.13
sFlt-1 (pg/ml)							
Maternal	43	15,979	11,915, 21,428	48	8,161	6,208, 10,729	0.004
Cord	24	3,166	1,165, 8,610	28	1,248	505, 3,087	0.23
PlGF (pg/ml)							
Maternal	43	43.2	23.7, 78.5	48	40.8	23.3, 71.1	0.90
sEng (ng/ml)							
Maternal	43	24.8	19.0, 32.4	48	13.5	10.6, 17.3	0.004

Bold denotes $p < 0.05$

When analyte comparisons were restricted to only African-American pregnancies, the associations of maternal sFlt-1 and sEng with preeclampsia remained significant. In addition, cord IGF-1 was significantly lower in preeclampsia pregnancies ($p = 0.02$).

Discussion

Prior studies have shown significantly higher concentrations of maternal anti-angiogenic factors [17, 18, 20, 21, 34, 35] and androgens (A4 and T) [32] in women with

preeclampsia compared to those with uncomplicated pregnancies. Our results are consistent with prior studies that were primarily conducted in predominantly Caucasian populations [17–25]. In addition, including maternal A4 and the anti-angiogenic factors simultaneously in the regression models did not alter the significance of the results, suggesting that both may be independently associated with preeclampsia.

In the cord samples, we found non-significantly lower levels of E3 and IGF-1 in samples from women with preeclampsia. Similar results have been reported in studies of Caucasian populations [36, 37]. When the cord analyses were restricted to only African-Americans, IGF1 was significantly lower in preeclamptic than in uncomplicated pregnancy.

This study has some limitations. The samples were collected at delivery, and measurements may not represent analyte concentrations earlier in pregnancy. Accounting for mode of delivery, however, did not alter the associations suggesting that the stress of a vaginal delivery did not affect concentrations. The CV for maternal sEng measures was high (29%), yet there was such a large difference in the mean sEng levels between the two groups that a significantly higher concentration was detected in maternal samples from preeclamptic pregnancies. It is likely that the real mean differences are even greater than reported here.

The strengths of the study include a large sample of African-Americans, a population that despite its higher risk has been less characterized than Caucasians with regard to concentrations of biomarkers in preeclampsia. To our knowledge, this also is the most comprehensive set of angiogenic factors, steroid sex hormones, and components of the IGF axis measured in both maternal and cord samples in a single preeclampsia study. This provided us with greater opportunity to explore both the in utero environment and maternal circulation in this condition.

The altered angiogenic balance and increased androgen concentrations reported here may also have implications for later health outcomes in the mother. Mothers with a history of preeclampsia and the female offspring from these pregnancies are at reduced risk of developing breast cancer [6, 7], and mothers (and possibly offspring) are at higher risk of cardiovascular disease later in life [1–5] when compared with mothers and offspring from normal pregnancies. Studies that have shown these associations of preeclampsia with later chronic disease risk have focused on either exclusively or predominantly Caucasian populations and did not stratify risk estimates by race/ethnicity [1, 2, 7, 38]. This is particularly surprising given the higher prevalence of risk factors for both preeclampsia and cardiovascular disease in African-American women [26, 28, 39, 40].

Currently, there is debate as to whether preeclampsia initiates a long-lasting, altered vascular state that contributes to later health outcomes or alternatively, if women who are

at higher risk of developing preeclampsia also have altered chronic disease susceptibility because of underlying risk factors in common across the conditions [2]. A prior study evaluating the association of preeclampsia (or gestational hypertension) with reduced risk of breast cancer reported that the reduction in risk was even stronger among women who had male offspring (relative risk 0.62, 95% CI, 0.47–0.82 for son compared to relative risk 0.75, 95% CI, 0.62–0.91 for whole population) [41]. This result was interpreted to “support the hypothesis that a protective effect of pre-eclampsia on breast cancer risk could originate from the particular pregnancy, rather than indicating an underlying biological trait that is protective against breast cancer in women who develop pre-eclampsia [41].” Additional studies focusing on predominantly non-Caucasian populations and/or that are large enough to explore the analyses by race and/or offspring gender may provide more insight into the relationship of preeclampsia with chronic disease risk.

Acknowledgments We would like to thank Lisa Philibert, RN and Kimberly Mandino, RN at LSUHSC-Shreveport for patient recruitment and clinical data collection for the study. We also thank Marianne Hyer and David Castenson at Information Management Systems for their contributions to data verification and analysis and Dr. Jun Zhang at NICHD for collaborating with us on the parent study. This research was supported in part by the intramural research program of the National Cancer Institute (NCI), National Institutes of Health and the Center for Cancer Training, Cancer Prevention Fellowship Program, NCI.

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