Null Results in Brief

Maternal Androgen and Estrogen Concentrations Are Not Associated with Blood Pressure Changes in Uncomplicated Pregnancies

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Abstract

Systolic blood pressure increase between the second and third trimester of pregnancy has been associated with a substantially reduced maternal breast cancer risk, and it has been suggested that elevated androgens mediate the association. Androgen and estrogen concentrations were measured in maternal serum collected in 86 uncomplicated, singleton pregnancies. Overall, there were no consistent or statistically significant patterns of association between the hormones and systolic, diastolic, or mean arterial blood pressure or blood pressure change between trimesters. Results were similar with adjustment for factors related to the hormones. These data are not consistent with the hypothesis that elevated androgen concentrations mediate the observed reduction in maternal breast cancer risk associated with increases in blood pressure over the pregnancy. (Cancer Epidemiol Biomarkers Prev 2006;15(10):2013–5)

Introduction

Certain pregnancy complications may be related to subsequent breast cancer risk, including preeclampsia, which seems protective (1). Data from the Child Health and Development Study showed a markedly reduced risk with elevated mean arterial pressure (MAP; ref. 2) and elevations in systolic blood pressure from mid to late pregnancy (3). Previous mechanistic investigations of the associations of pregnancy characteristics and breast cancer risk have centered on estrogen exposure (4, 5), and some have focused on androgens (1, 3, 4, 6). We explored the possibility that maternal hormones mediate this substantial decrease in breast cancer risk observed with blood pressure increases during pregnancy (7).

Materials and Methods

Data were from a longitudinal preeclampsia study conducted at the University of Pittsburgh (Pittsburgh, PA; ref. 8) that included all women who attended the Magee Womens Hospital's obstetric practice, delivered between February 1994 and May 1998, and agreed to participate. Eligible for analysis were controls from a previous case-control study of preeclampsia with singleton pregnancies, and without preexisting diabetes or hypertension (n = 86; ref. 4). Informed consent for a questionnaire, interview, and blood collection was obtained from all study participants.

Maternal blood was collected at admission for labor and delivery. The hormone assays have been described (9). Briefly, dehydroepiandrosterone sulfate and unconjugated concentrations of estradiol, androstenedione, testosterone, and estriol were measured in serum by RIA. The coefficients of variation based on blinded quality control samples were 8.5% for dehydroepiandrosterone sulfate, 10.2% for androstenedione, 9.6% for testosterone, 13.7% for estradiol, and 6.8% for estriol.

Information was obtained from medical records. Blood pressure was measured at each prenatal visit between 4 and 41 weeks of gestation. There were 104 measurements in the first, 257 in the second, and 534 in the third trimester, with the number per subject ranging from 1 to 19 (median, 11). Mean diastolic and systolic blood pressure and MAP [diastolic pressure + 1/3 (systolic blood pressure − diastolic blood pressure)] were calculated. To replicate the variable for blood pressure change used in the breast cancer study (3), we subtracted the first diastolic, systolic, or MAP measurement in the second trimester from the last measurement in the third trimester and divided by the number of weeks between. Change between trimesters was divided into three categories: < = 0 (indicating that blood pressure either remained the same or decreased between trimesters), and the remaining observations were split at their median. Blood pressure change between the first and second and the first and third trimesters was calculated similarly.

The hormones were logarithmically transformed to remove skewness from their distributions. Mean hormone concentrations were determined by blood pressure categories using analysis of covariance, and geometric means and 95% confidence intervals are presented. Confounding was assessed by adding covariates individually to linear regression models with the hormones as dependent variables. Covariates included maternal age, pre-pregnancy weight, height (continuous variables), and race/ethnicity, parity, and offspring's sex (categorical variables). Tests of the trends in hormones with blood pressure categories were evaluated using ordinal variables. Statistical significance was defined as $P < 0.05$ (two sided).

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Results

The women were in their mid-20s (mean, 26.2 years). Mean length of gestation was relatively short (37.8 weeks with the median closer to 39 weeks) because, in the initial study, controls were matched to preeclampsia cases by pregnancy length. About 60% were Caucasian and 40% were African-American. Forty percent were primigravid and 73% were nulliparous.

Table 1 presents mean hormone concentrations by blood pressure in the second and third trimesters and by blood pressure change between trimesters. Overall, the data showed no consistent, statistically significant patterns in the associations. However, after adjustment for age and race, androstenedione was significantly associated with higher average second trimester systolic blood pressure (P for trend = 0.04). This finding was not observed for second trimester diastolic pressure or MAP or for third trimester blood pressure. Furthermore, there were no associations between the hormones and blood pressure change from the second to third trimesters. The hormones were not associated with average blood pressure over the entire pregnancy or in the first trimester or with blood pressure change between the first and second or first and third trimesters (data not shown). These results remained with adjustment for maternal and pregnancy factors known to be related to the hormones in these data (data not shown).

Discussion

Previously, a strongly linear reduction in maternal breast cancer risk was shown with increases in systolic blood pressure between the second and third trimester (3), and the exposure of the breast to altered pregnancy hormone concentrations has been proposed as a possible mechanism. Our results are not consistent with this hypothesis, as we found no association of androgens or estrogens with systolic pressure change from mid to late pregnancy.

Our study was limited in statistical power as indicated by the wide confidence intervals. For this reason, we focused on the a priori hypothesis raised by Cohn et al. in interpreting our data and assessed overall patterns.

Table 1. Mean hormone concentrations (95% confidence interval) by category of blood pressure during the second and third trimesters and change in blood pressure between the second and third trimesters

	n	DHEAS (μg/dL)	Androstenedione (ng/dL)	Testosterone (ng/dL)	Estradiol (pg/mL)	Estriol (ng/mL)
Average for second trimester						
Diastolic (mmHg)						
<68	26	96.5 (64.4-145)	414 (304-563)	189 (134-267)	16,710 (12,276-22,746)	13.8* (10.6-17.8)
68-71	26	81.0 (59.0-111)	353 (277-449)	143 (109-187)	24,664 (19,369-31,407)	20.7* (16.9-25.3)
>71	26	104 (69.4-154)	304 (224-412)	130 (92.7-183)	24,464 (18,031-33,192)	16.1 (12.4-20.7)
P for trend		0.46	0.92	0.71	0.22	0.81
Systolic (mmHg)						
<112	26	70.5 (46.9-106)	255* (187-348)	101*,† (71.2-142)	28,834 (21,147-39,316)	23.3*,† (18.0-30.3)
112-118	26	108 (78.7-149)	344*,† (269-439)	161* (122-211)	19,057 (14,919-24,344)	14.1* (11.4-17.3)
>118	26	106 (72.5-155)	506*,† (379-675)	217*,† (158-300)	18,349 (13,749-24,487)	13.9*,† (10.9-17.8)
P for trend		0.26	0.06	0.06	0.99	0.24
MAP (mmHg)						
<83	26	91.8 (51.0-165)	360 (229-564)	182 (129-257)	23,445 (14,356-38,289)	17.5 (11.2-27.4)
83-86	25	125 (82.4-190)	422 (307-580)	147 (87.9-246)	23,754 (16,780-33,626)	17.8 (13.0-24.4)
>86	27	91.0 (49.1-169)	304 (190-487)	149 (96.1-229)	22,557 (13,479-37,748)	15.8 (9.9-25.2)
P for trend		0.55	0.26	0.20	0.30	0.92
Average for third trimester						
Diastolic (mmHg/wk)						
<70	28	98.5 (66.9-145)	392 (292-527)	161 (115-223)	23,036 (17,148-30,946)	18.6 (14.5-23.8)
70-73	28	85.7 (59.2-124)	279* (211-370)	134 (97.7-184)	19,090 (14,391-25,323)	14.8 (11.7-18.7)
>73	28	95.9 (70.9-130)	405* (322-510)	164 (126-212)	22,927 (18,204-28,875)	16.6 (13.7-20.2)
P for trend		0.42	0.25	0.69	0.44	0.88
Systolic (mmHg/wk)						
<114	28	106 (72.3-156)	323 (241-433)	136 (98.1-189)	16,820 (12,531-22,577)	12.1*,† (9.5-15.5)
114-120	28	87.1 (58.4-130)	379 (280-515)	148 (105-208)	27,816 (20,506-37,732)	22.3* (17.3-28.9)
>120	28	87.3 (64.6-118)	362 (288-456)	174 (135-225)	21,550 (17,120-27,127)	16.9*,† (13.9-20.5)
P for trend		0.69	0.99	0.52	0.23	0.39
MAP (mmHg)						
<84	28	102 (60.5-172)	368 (247-548)	148 (96.1-229)	21,555 (13,935-33,341)	16.7 (11.2-24.8)
84-89	28	81.0 (54.0-122)	332 (243-452)	155 (111-218)	23,227 (16,560-32,580)	16.5 (12.2-22.5)
>89	28	126 (69-231)	378 (238-599)	168 (101-277)	25,091 (15,156-41,538)	17.8 (11.2-28.1)
P for trend		0.78	0.96	0.58	0.22	0.53
Change from second to third trimester						
Diastolic (mmHg/wk)						
≤0	26	109 (83.0-144)	336 (266-424)	140 (109-180)	24,022 (19,470-29,638)	15.5* (12.8-18.7)
0.1-0.45	26	91.3 (70.1-119)	410 (328-512)	174 (137-220)	24,319 (19,895-29,728)	20.1*,† (16.8-24.1)
>0.45	26	88.5 (66.4-118)	311 (245-396)	137 (105-177)	18,576 (14,942-23,093)	15.2*,† (12.5-18.4)
P for trend		0.50	0.51	0.85	0.11	0.74
Systolic (mmHg/wk)						
≤0	28	74.8* (57.1-97.9)	359 (286-450)	154 (120-196)	20,411 (16,639-25,040)	17.1 (14.3-20.6)
0.1-0.54	23	111* (84.0-147)	377 (297-477)	167 (130-216)	19,911* (16,083-24,651)	14.9* (12.3-18.0)
>0.54	25	106 (80.6-140)	318 (252-401)	129 (101-166)	26,701* (21,629-32,963)	18.5* (15.3-22.4)
P for trend		0.13	0.31	0.26	0.29	0.75
MAP (mmHg/wk)						
≤0	23	118 (77.4-181)	411 (297-568)	184 (129-262)	24,130 (16,924-34,403)	14.0 (10.2-19.4)
0.1-0.44	26	90.1 (62.0-131)	349 (262-465)	145 (107-199)	23,686 (17,333-32,369)	20.0 (15.1-26.6)
>0.44	27	98.0 (58.4-164)	321 (217-477)	145 (94.0-222)	21,979 (14,288-33,811)	17.5 (11.8-25.9)
P for trend		0.98	0.15	0.16	0.30	0.37

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; MAP, mean arterial pressure.
*,† Means are significantly different at the $P < 0.05$ level.

Preeclampsia has been associated with a 20% decrease in breast cancer risk (10, 11). Thus, the 50% risk reduction observed in women with smaller increases in blood pressure not indicative of preeclampsia is surprising (3). Given this, replication of Cohn et al.'s finding is needed. If real, however, the implication may be that the observed protection could be related to cardiovascular factors rather than to the specific placental abnormalities that are seen in preeclampsia. Perhaps in support of this, blood pressure changes in Cohn et al.'s (3) analysis were not related to placental abnormalities.

In summary, our findings of no association between several androgens and estrogens and blood pressure change between the second and third trimester are not consistent with alterations in pregnancy hormones mediating the strongly reduced breast cancer risk observed with blood pressure increases. Lack of association in these data argues for expanding investigations of the underlying biology to other mechanisms.

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