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Tall or Short? Twenty Years after Preeclampsia Exposure *In Utero*: Comparisons of Final Height, Body Mass Index, Waist-to-Hip Ratio, and Age at Menarche among Women, Exposed and Unexposed to Preeclampsia during Fetal Life

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ABSTRACT

Women exposed to preeclampsia during fetal life have lower risk of breast cancer, compared with unexposed women, possibly through fetal programming. Hypothetically, preeclampsia exposure could affect well-known risk factors for breast cancer, such as pubertal development or adult anthropometry. Women born in a defined geographic area of Sweden from 1973 through 1978, with verified preeclampsia exposure ($n = 230$) and nonexposure ($n = 359$) during fetal life, answered questions about anthropometric measures, smoking, parity, and age at menarche in a telephone interview in early adulthood. Compared with unexposed offspring, female offspring of women who had preeclampsia were lighter and shorter for gestational age, but in young adulthood there were no differences in height, body mass index, waist-to-hip ratio, or age at menarche. When analyzing the effects of other maternal and fetal characteristics, the results indicate that approximately 50% of the variance in final height was explained by parental heights and birth length for gestational age. Young-adult body mass index was weakly associated with maternal body mass index, maternal smoking, and birth weight for gestational age, which together explained 12% of the variance. Neither of the assessed maternal or fetal characteristics were significantly associated with age at menarche or waist-to-hip ratio. These data indicate that neither adult anthropometry nor age at menarche is in the causal pathway between intrauterine preeclampsia exposure and the reduced risk of breast cancer. **(*Pediatr Res* 49: 763–769, 2001)**

Abbreviation:
BMI, body mass index

Women exposed to preeclampsia during their fetal life are reported to have decreased risk of breast cancer (1, 2). Other well-known risk factors for breast cancer are early menarche and tall stature (3, 4). Both the association between preeclampsia and breast cancer and the association between early menarche or tall stature and breast cancer have been hypothesized to be caused by intrauterine estrogen exposure (5–7). Therefore, one reasonable hypothesis is that preeclampsia exposure could affect well-known risk factors for breast cancer, such as pubertal development or adult anthropometry, which in turn are important for breast cancer development.

Birth characteristics and adult central obesity are also reported to be associated with breast cancer, coronary heart disease, insulin resistance, and hypertension (8–13), but whether intrauterine exposure to preeclampsia influences the adult fat distribution of growth-restricted individuals is presently not known.

To better understand the biologic pathway for how the intrauterine environment might influence adult morbidity, we assessed the effects of preeclampsia exposure and birth characteristics on known risk factors for breast cancer, such as final height, difference from target height, BMI, waist-to-hip ratio, and age at menarche.

METHODS

We used the Swedish Medical Birth Register to select every female offspring of women with preeclampsia, born during 1973 through 1978 in a defined geographic area of Sweden

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Table 1. *Comparison of maternal and fetal characteristics of the preeclampsia-exposed and -unexposed women, born 1973 through 1978, in Sweden*

	Preeclampsia			
	Exposed (n = 230)		Unexposed (n = 359)	
Maternal fetal characteristics	*n*	%	*n*	%
Age (y)				
<30	179	77.8	285	79.4
30–34	39	17.0	62	17.3
>34	12	5.2	12	3.3
Parity				
0	151	65.7	187	52.1
1–2	69	30.0	157	43.7
>2	10	4.3	15	4.2
Induced abortions				
0	203	93.1	309	87.8
≥1	15	6.9	43	12.2
Missing	12		7	
Spontaneous abortions				
0	183	83.9	302	85.8
≥1	35	16.1	50	14.2
Missing	12		7	
Height (cm)				
<160	32	13.9	44	12.3
160–164	72	31.3	89	24.9
165–169	68	29.6	120	33.5
170–174	43	18.7	87	24.3
≥175	15	6.5	18	5.0
Missing	0		1	
Weight at first antenatal visit (kg)				
≤55	65	28.9	118	33.2
56–69	95	42.2	185	52.1
70–79	34	15.1	39	11.0
≥80	31	13.8	13	3.7
Missing	5		4	
BMI				
<19.8	46	20.4	87	24.6
19.8–26.0	122	54.2	237	67.0
26.1–29.0	26	11.6	19	5.3
≥29.1	31	13.8	11	3.1
Missing	5		5	
Daily smoking				
No	154	73.7	184	55.1
Yes	55	26.3	150	44.9
Missing	21		25	
Prepregnancy diseases				
Essential hypertension	9	4	0	0
Gestational age (wk)				
≤36	36	15.8	13	3.6
37–41	177	78.0	314	87.5
≥42	14	6.2	32	8.9
Missing	3		0	
Birth weight (g)				
<2500	63	27.6	12	3.4
2500–2999	51	22.4	49	13.9
3000–3499	50	21.9	129	36.4
3500–3999	46	20.2	114	32.2
≥4000	18	7.9	50	14.1
Missing	2		5	
Birth weight for gestational age (SD)				
<−2	59	26.1	10	2.8
−2 to −1.1	46	20.4	58	16.2
−1 to 0.9	101	44.7	239	66.6
1.0–1.9	13	5.7	45	12.5
≥2	7	3.1	7	1.9
Missing	4		0	

Table 1. *Continued*

Maternal fetal characteristics	Preeclampsia			
	Exposed (n = 230)		Unexposed (n = 359)	
	n	%	n	%
Birth length (cm)				
≤45	44	19.8	10	2.8
46–47	35	15.8	31	8.7
48–49	53	23.9	80	22.4
50–51	47	21.2	150	42.0
≥52	43	19.3	86	24.1
Missing	8		2	
Birth length for gestational age (SD)				
<−2	37	16.8	12	3.4
−2 to −1.1	51	23.2	46	1.9
−1 to 0.9	105	47.7	244	68.4
1–1.9	22	10.0	44	12.3
≥2	5	2.3	11	3.0
Missing	10		2	

(including Stockholm, Uppsala, Västerås, Falun, Mora, Örebro, and Bollnäs) with about one third of the Swedish population. A cohort unexposed to preeclampsia was created by a random sample of two female offspring per exposed individual, matched by year and hospital of birth. The second unexposed individual was included only if the record of the first selected was not found when unit records later were scrutinized. Only single births were selected.

Measurements of exposures. The Birth Register contains >99% of all births in Sweden (14). Of the women we selected from the register, we were able to retrieve information from individual antenatal and obstetrical records for 99%. All women had attended antenatal care and followed the standardized routines. In antenatal records, information is prospectively collected from the first to the last antenatal visit. At registration to antenatal care, we obtained information about maternal height, weight, parity, number of previous induced and spontaneous abortions, cigarette smoking, prepregnancy diseases, the date of the first day in the last menstruation, and blood pressure. During pregnancy, blood pressure and proteinuria were measured on a regular basis. After 24 wk gestation, there were visits to the midwife scheduled every second week up till 36 wk, and every week thereafter.

Diagnoses of hypertensive diseases during pregnancy were classified according to the Swedish version of *International Classification of Diseases, 8th revision* (ICD-8 codes 637.03, 637.04, 637.09, and 637.99). To verify exposure status, all individual antenatal and obstetrical records were scrutinized by one of us (H.S.R.) using a structured protocol. Information on the delivery, including inpatient care, mode of delivery, maternal and fetal complications, fetal anthropometry, Apgar score, and health status, was also obtained from the individual records. Birth weight and birth length for gestational age were calculated according to Swedish reference standards, based on births from the 1970s, with gestational age calculated from the date of the last menstruation (15). Before validation of the individual records, approvals from every head of the departments were received.

Mild preeclampsia is defined as a diastolic blood pressure from 90 to 109 mm Hg combined with proteinuria of 0.3–4.9 g/d or 1+ or 2+ on a urine dipstick, occurring during pregnancy. Severe preeclampsia is defined as preeclampsia with either a diastolic blood pressure of ≥110 mm Hg or proteinuria of ≥5 g/24 h or both. The diagnostic criteria correspond to the criteria proposed by the National High Blood Pressure Education Program Working Group (16). We regarded preeclampsia exposure as too short if the symptoms had occurred the day before delivery or later. Therefore, only women whose mothers had symptoms for ≥2 d before birth were included as being exposed to preeclampsia. After validation of the individual records, we identified 287 pregnancies with preeclampsia, and the unexposed group consisted of 486 individuals.

End point variables. Data on the adult anthropometry of the offspring were retrieved from personal telephone interviews, performed by professional female interviewers during the period November 1997 through April 1998. Before the interview, a brochure with an invitation to participate in the study was sent by mail. Information about the study, some of the questions, a measuring-tape, and instructions with a picture of where and how to measure were also enclosed. The young women, 20 to 25 years old by that time, were asked to measure their height, weight, waist circumference at the level of the umbilicus, and hip circumference at its widest location while standing. They were also asked about age at menarche, parity, and parental heights. The interviewers had no information about exposure status of the individuals or the hypotheses of the study.

In the preeclampsia-exposed cohort (n = 286), 34 women (12%) were lost to follow-up owing to unknown address or telephone number or no answer, and 22 (8%) refused to participate, yielding a response rate of 80%. In the unexposed cohort (n = 451), 51 women (11%) were lost to follow-up owing to unknown address or telephone number or no answer, and 41 (9%) refused to participate, yielding a response rate of 80%. Mean age (23.5 y) and the number of pregnancies were the same in the exposed and unexposed groups. The propor-

tions of smokers were 20.9% and 17.8% in the exposed and unexposed groups, respectively.

Calculation of target height was performed by using the formula target height = 37.85 + 0.75 (mid-parental height), as proposed by Luo *et al.* (17). BMI is defined as weight (in kilograms) divided by height squared (m^2), and waist-to-hip ratio is waist circumference divided by hip circumference.

Statistical analyses. Mean values for the end point variables final height, difference from target height, BMI, waist-to-hip ratio, and age at menarche were compared between the exposed and the unexposed cohorts. We performed ANOVA by Scheffé to compare means in more than two groups (for example unexposed, mild preeclampsia, and severe preeclampsia), and $p > 0.05$ (two-sided) was considered not significant. For prediction of final height, difference from target height, and BMI, we performed multiple linear regression using the SAS statistical package (18).

Permission to perform the study was granted by the Ethical Committee at the Medical Faculty, Uppsala University, Sweden.

RESULTS

Table 1 shows comparisons of maternal and fetal characteristics between the group of women who were exposed to preeclampsia and the group of unexposed women. The proportions of nulliparous mothers, mothers with high weight, and nonsmokers were larger in the preeclampsia-exposed group compared with the unexposed group. The proportions of women with low gestational age, low birth weight, and short birth length were larger in the exposed group compared with the unexposed group.

In Table 2, fetal and adult mean anthropometries are compared between exposed and unexposed groups. Exposure status is analyzed in two levels: mild and severe preeclampsia. Compared with the unexposed group, mean gestational age was significantly younger and mean birth weight and birth length for gestational age are significantly smaller for those exposed to mild or severe preeclampsia. There were no significant differences in mean final height, difference from target height, age at menarche, BMI, or waist-to-hip ratio between young women exposed or unexposed to preeclampsia during fetal life.

Table 3 presents the effects of maternal characteristics (height, BMI, and smoking) and birth characteristics (gestational age, birth weight, and length for gestational age) on final height, difference from the target height, and BMI. Maternal height, birth weight, and birth length for gestational age were significantly associated with final height and difference from target height. Maternal BMI, maternal smoking, and birth weight for gestational age were significantly associated with adult BMI. Neither of the independent variables in Table 3 influenced age at menarche or waist-to-hip ratio (data not shown).

Multiple linear regression was performed to estimate the effects of maternal and fetal characteristics on the final height, difference from target height, and BMI. In Table 4, only the best model for each outcome variable is presented (*i.e.* with only significant factors in the model). Final height was predicted by parental heights and birth length for gestational age, which explained 47% of the variance in height. The variable estimates indicate that the predicted final height increases approximately 0.3 cm/cm increase in each parental height increase, and 1.5 cm per increase in SD in birth length for gestational age. The ability to reach target height (calculated from parental height) was only predicted from birth length for gestational age, which explained 12.6% of the variance. BMI in young women was partly (12.2% of the variance) explained by maternal BMI, maternal smoking, and birth weight for gestational age. For each SD increase in birth weight for gestational age, there was an increase in BMI of 0.29 kg/m^2.

DISCUSSION

In the present population-based cohort study, we evaluated 230 women who were exposed to preeclampsia *in utero* and 359 randomly selected unexposed women and compared adult anthropometry and age at menarche. Intrauterine exposure to preeclampsia did not significantly influence final height, BMI, waist-to-hip ratio, or age at menarche. These data indicate that adult anthropometric measures and age at menarche are not in

Table 2. *Comparison of fetal and adult anthropometry (expressed as mean values) among preeclampsia-exposed and -unexposed women, born 1973 through 1978, in Sweden*

	No preeclampsia (n = 359)		Mild preeclampsia (n = 135)		Severe preeclampsia (n = 95)	
Characteristic	mean	SD	mean	SD	mean	SD
Gestational age (wk)	40.2	1.5	39.6*	2.1	38.2*	2.3
Birth weight for gestational age (SD)	−0.1	1.0	−0.8*	1.6	−1.3*	1.2
Birth length for gestational age (SD)	−0.1	1.1	−0.5*	1.4	−0.8*	1.4
Final height (cm)	168.0	6.3	167.3	7.0	166.9	6.8
Difference final height-target height (cm)	−0.5	5.1	−0.1	4.7	0.4	5.4
Age at menarche (y)	13.1	1.4	12.8	1.5	13.0	1.4
BMI	22.8	3.8	22.8	3.7	22.0	3.3
Waist-to-hip ratio	0.79	0.08	0.80	0.08	0.80	0.07

* Significantly different from unexposed ($p < 0.05$).

Table 3. *Comparison of final height, differences from target height, and BMI according to paternal height and maternal and fetal characteristics*

Independent variable	*n*	Mean final height (cm)	*p* value	Mean final height-target height	*p* value	Mean BMI	*p* value
Paternal height (cm)							
<171	70	163.0	0.0001	1.1	NS	22.8	NS
171–175	124	165.0		0.2		22.5	
176–180	166	167.3		0.1		22.4	
181–185	118	169.3		0.5		22.5	
>185	88	174.0		1.2		23.2	
Maternal height (cm)							
<160	77	161.9	0.0001	−1.1	0.0059	22.7	NS
160–164	161	165.4		0.0		22.5	
165–169	188	168.7		1.3		22.5	
170–174	130	170.7		0.3		22.9	
≥175	33	174.1		1.0		22.7	
Maternal BMI							
<19.8	133	167.2	NS	−0.2	NS	21.9	0.0001
19.8–26.0	359	167.6		0.5		22.4	
26.1–29.0	45	168.3		0.5		25.0	
≥29.1	43	168.6		1.24		24.8	
Maternal smoking (cigarettes/day)							
0	338	167.9	NS	0.5	NS	22.2	0.0002
<10	60	168.8		1.6		23.5	
≥10	145	167.0		−0.2		23.6	
Gestational age (wk)							
<37	46	166.7	NS	0.1	NS	21.9	NS
37–41	494	167.8		0.5		22.6	
≥42	46	167.7		0.1		23.7	
Birth weight for gestational age (SD)							
<−2.0	70	163.6	0.0001	−2.0	0.0001	22.2	0.0022
−2.0 to −1.1	103	165.4		−1.1		22.3	
−1.0 to 0.9	340	168.3		0.8		22.5	
1.0–1.9	58	171.8		2.7		23.5	
≥2	14	171.4		2.6		25.9	
Birth length for gestational age (SD)							
<−2.0	49	163.1	0.0001	−2.8	0.0001	22.6	NS
−2.0 to −1.1	97	164.9		−1.5		22.7	
−1.0 to 0.9	349	168.0		0.7		22.5	
1.0–1.9	66	172.0		3.2		23.0	
≥2	16	172.9		3.9		25.8	

the causal pathway between intrauterine exposure to preeclampsia and decreased risk of breast cancer. Variance in final height was to a large extent explained by parental heights and birth length for gestational age.

Information about exposure status was obtained from prospectively collected data in individual antenatal and obstetrical records, starting at the women's mothers' first visit to antenatal care. Women with verified exposure or nonexposure to pre-

Table 4. *Multiple linear regression modeling for prediction of final height, difference from target height, and BMI by maternal and fetal characteristics*

Independent variables	Adjusted R^2*	*B*	*SE B*	β	*p*
Maternal height		0.4	0.04	0.34	0.0001
Paternal height		0.3	0.03	0.37	0.0001
Birth length for gestational age		1.5	0.16	0.29	0.0001
Model predicting final height	0.47				0.0001
Birth length for gestational age		1.4	0.2	0.36	0.0001
Model predicting difference from target height	0.13				0.0001
Maternal BMI		0.3	0.04	0.27	0.0001
Maternal smoking		0.1	0.03	0.18	0.0001
Birth weight for gestational age		0.3	0.12	0.11	0.0075
Model predicting BMI	0.12				0.0001

* Adjusted R^2 denotes the adjusted proportion of the variance explained by the model.

B denotes the variable estimate.

SE B denotes the standard error of the variable estimate.

β denotes the standardized estimate.

eclampsia during fetal life were then interviewed >20 y later. The proportion lost to follow-up was only 20% in both groups. To avoid introduction of recall bias, professional interviewers, who were blinded to exposure status, performed the interviews. Although the study subjects themselves measured some end point variables (weight, height, and waist and hip circumferences), it is highly unlikely that any possible measurement error differs by exposure status.

Altered placental function is described in preeclampsia, and several hormonal factors that may relate preeclampsia to decreased risk of breast cancer have been reported: reduced levels of estrogens (19) and IGF-1 (20), and increased levels of progesterone (21) and androgens (19, 22). These factors may influence the offspring through programming, which hypothetically would alter age at menarche or final height. However, there was no effect of preeclampsia on final height or age at menarche, although the mean birth length for gestational age was significantly shorter among daughters of women with preeclampsia. Preeclampsia is probably influenced by genetic factors (23), and one may only speculate whether there may be genetically determined alterations in both the placental and fetal hormonal synthesis, which in turn protects the female fetus against subsequent risk of breast cancer.

The mean birth length for gestational age was significantly shorter among the preeclampsia-exposed women, but they reached the same final height as the unexposed women. Preeclampsia is associated with low birth weight, which in turn is reported to predispose to central obesity (high BMI combined with high waist-to-hip ratio), hypertension, coronary heart disease, and insulin resistance, hypothetically because of fetal programming (24–27). Alternatively, as proposed by Hatterslay and Tooke (28), the association between fetal and adult anthropometry is explained mainly by genetic factors. In the present study, preeclampsia-exposed and -unexposed individuals did not differ in BMI or waist-to-hip ratio in early adulthood. Inasmuch as preeclampsia is associated with hypertension and insulin resistance (29), it is important, as previously suggested (30, 31), to include the underlying causes of low birth weight in studies of adult morbidity.

Neither age at menarche nor waist-to-hip ratio were significantly affected by any maternal or infant characteristics. It was recently reported that birth length for gestational age is a better predictor than birth weight for gestational age for the final height in men (32), which is in agreement with our results. We were also able to retrieve data on parental height, and approximately 50% of the variance in final height could be explained by birth length for gestational age and parental height. For young-adult BMI there were weak associations with maternal BMI, maternal smoking, and birth weight for gestational age, which only explained 12% of the variance. In contrast to a previous report (33), we found no indication of an association between low birth weight and adult abdominal obesity. This may be because the underlying cause for low birth weight in the present study was preeclampsia.

In conclusion, the results in the present study suggest that exposure to preeclampsia during fetal life does not influence age at menarche or anthropometric measures in young adults. Thus, prenatal exposure to preeclampsia and adult anthropometry should be regarded as independent risk factors in causative studies of breast cancer.

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