AMERICAN JOURNAL OF HUMAN BIOLOGY 18:133–140 (2005)

Original Research Article

High Ponderal Index at Birth Predicts High Estradiol Levels in Adult Women

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ABSTRACT Inter-individual variation in levels of sex hormones results from differences in genetic, developmental, and environmental factors. We tested a hypothesis that programming of the fetal neuroendocrine axis may predispose some women to produce higher levels of steroid hormones during their menstrual cycles as adults. One hundred forty-five regularly menstruating 24- to 36- year-old women collected daily saliva samples for one menstrual cycle. Data on women's birth weights and birth lengths were obtained from medical records. A positive relationship was observed between ponderal index at birth (an indicator of nutritional status, calculated as birth weight/(birth length)^3) and levels of estradiol (E2) in menstrual cycles, after controlling for potential confounding factors. Mean E2 was 16.4 pmol/l in the low ponderal index tertile, 17.3 pmol/l in the moderate ponderal index tertile, and 19.6 pmol/l in the high ponderal index tertile (the high ponderal index group had significantly higher E2 than both low and moderate ponderal index groups, $P = 0.0001$). This study shows a positive association between ponderal index recorded for women at birth and levels of E2 measured during their menstrual cycles as adults. This suggests that conditions during fetal life influence adult production of reproductive hormones and may contribute to inter-individual variation in reproductive function. In addition, because large size at birth is one of the factors linked with an increased risk of breast cancer, our findings provide a physiological link for the observed positive relationship between indicators of energetic conditions during fetal growth and breast cancer in women. Am. J. Hum. Biol. 18:133–140, 2006.

Considerable variation in levels of sex steroid hormones has been described both among individual women and among populations (Ellison et al., 1993; Jasienska and Thune, 2001), and several factors have been proposed to account for such variation. These include factors related to energy availability and metabolism, especially physical activity and weight loss (Ellison and Lager, 1986; Jasienska and Ellison, 1998, 2004). Genetic variation underlying steroid hormone metabolism has been implicated as another source of variation in endogenous hormonal levels (Feigelson et al., 1998).

Conditions during intrauterine growth and development influence adult physiology (Crespi and Denver, 2005; Ellison, 2005; Horton, 2005; Jones, 2005; Kuzawa, 2005; Lampl, 2005; McDade, 2005; Pike, 2005; Worthman and Kuzara, 2005) and are related to the risk of major chronic diseases, including cardiovascular diseases and diabetes (Barker, 1995; Forsen et al., 1997) and also breast cancer in women. Several studies [but not all; see: Ekbom et al. (1997), Sanderson et al. (2002), and Titus-Ernstoff et al. (2002)] have shown that the risk of breast cancer increases with increasing birth weight (Ahlgren et al., 2004; Andersson et al., 2001; De Stavola et al., 2000; Ekbom et al., 1992; Hubinette et al., 2001; Innes et al., 2000; Mellemkjaer

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Received 8 May 2005; Revision received 8 October 2005; Accepted 31 October 2005

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajhb.20462

et al., 2003; Michels, 1996), which is believed to be an indicator of conditions during fetal development. It is well established that lifetime exposure to high levels of steroid hormones, especially estradiol, increases the risk of breast cancer (Pike et al., 1993). Lifetime exposure results partly from the levels of estradiol produced during menstrual cycles (Jasienska et al., 2000). Our results suggest that intrauterine environment may also contribute to variation in levels of endogenous estradiol and may, therefore, provide an explanation of the observed relationship between factors describing fetal conditions and risk of breast cancer in women.

MATERIALS AND METHODS

Study group

Subjects for the study were women from Poland recruited for the study by advertisements, from June 2001 to June 2003. Women were selected for participation if they met the following criteria: age between 24 and 36 years, regular menstrual cycles and no fertility problems, no gynecological and/or chronic disorders (i.e., diabetes, hypo/hyperthyroidism), not taking any hormonal medication or using hormonal contraception during the 6 months before recruitment, and not being pregnant or lactating during the 6 months before recruitment. Recruited women signed a consent form after being informed about the aims and requirements of the study, which had been approved by the Jagiellonian University Research Ethics Committee. Out of 186 women who collected saliva samples for an entire menstrual cycle, we obtained data for 145 of them on both birth weight and birth length. Because the day of the midcycle 17β-estradiol (E2) drop could not be reliably identified for 9 subjects, their data were excluded from analyses that used aligned E2 data. Therefore, we used data from 145 women for nonaligned E2 analyses and data from 136 women for aligned E2 analyses.

Anthropometric measurements, general questionnaire, and birth characteristics

Subjects' body weight, height, subscapular and triceps skinfolds, and percent body fat (by bioimpedance) were measured by a trained anthropologist. A general questionnaire (partly by interview and partly self-administered) was used to collect information on education, reproductive history, and past use of hormonal medication, tobacco, and alcohol. Data on birth weight and birth length were obtained from subjects' personal "health books," which contain records about the individual's birth size, health condition at birth, and any parturition problems.

Estradiol indices and assay procedure

Women collected daily morning saliva samples for one entire menstrual cycle. Saliva samples from 20 days (reverse cycle days −5 to −24, where the last day of each cycle was marked as day −1) of each cycle were analyzed for the concentration of E2 using an ^{125}I-based radioimmunoassay kit (#39100, Diagnostic Systems Laboratories, Webster, TX) with published (Jasienska et al., 2004) modifications to the manufacturer's protocol. The sensitivity of the estradiol assay is 4 pmol/l. Average intra-assay variability was 9%, and inter-assay variability ranged from 23% for lower (15 pmol/l) to 13% for higher (50 pmol/l) values. The "mean non-aligned E2" (mean of reverse cycle days −5 to −24) was calculated from 20 consecutive cycle days. Prior to other statistical analyses, cycles were aligned based on identification of the day of the midcycle E2 drop (day 0, Fig. 1), which provides a reasonable estimate of the day of ovulation (Lipson and Ellison, 1996). E2 values from 18 consecutive days of each cycle aligned on day 0 were used in analyses. The following E2 indices were calculated from the aligned data: "mean E2" (mean of days −9 to +8), "mean midcycle E2" (mean of days −2 through +2), "mean luteal E2" (mean of days 0 through +8), "cycle day 0" (E2 value on day 0), and "cycle day −1" (E2 value on pre-ovulatory day) (Fig. 1).

Statistical analysis

The relationship between birth weight and indices of E2 was tested in multiple regression analyses. As independent variables, we also included factors that may act as potential confounders, such as age, age at menarche, body weight, body height, number of cigarettes smoked daily, and units of alcohol consumed per week. We performed the same analyses with ponderal index instead of birth weight as the independent variable. Ponderal index was calculated as birth weight/(birth length)^3 and expressed in kg/m^3.

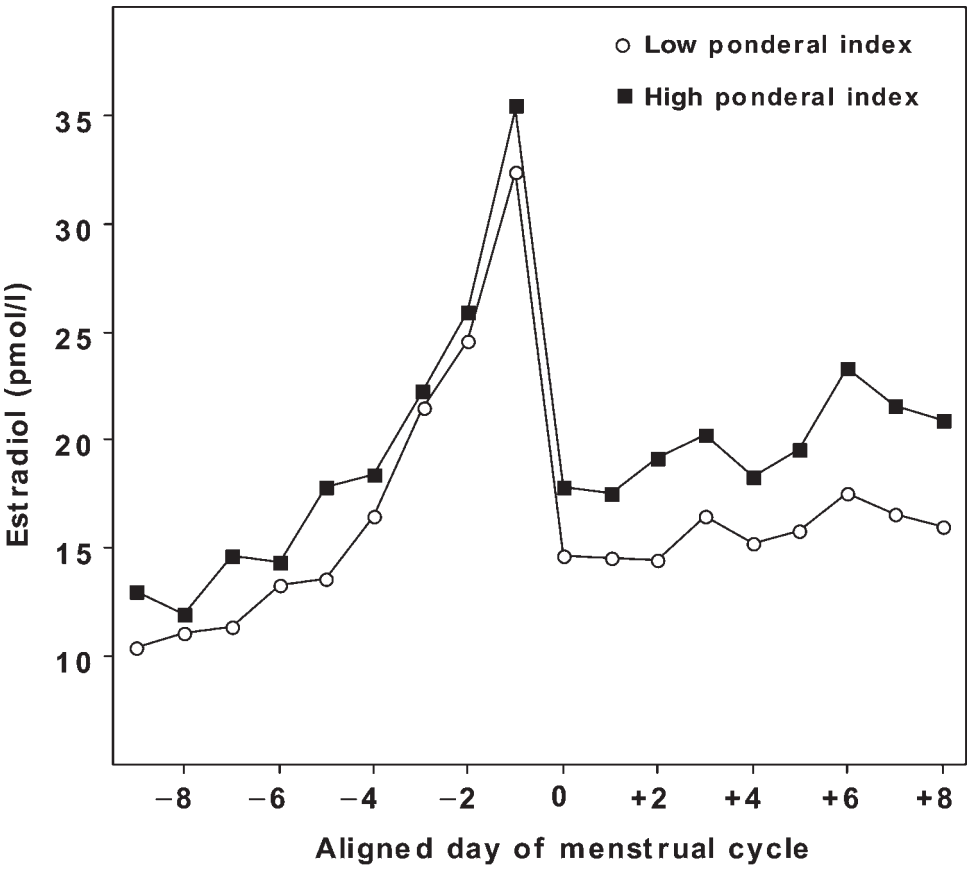

Fig. 1. Estradiol profiles in groups of women with low and high ponderal index at birth. Division into groups is based on tertiles of the ponderal index. The group based on the 2nd tertile and the confidence intervals are omitted for clarity.

In addition, women were divided into 3 groups based on tertiles of the ponderal index (all women having the same ponderal index were included in the same tertile; therefore groups do not have the same number of subjects). Differences among the low ponderal index, moderate ponderal index, and high ponderal index groups in birth weight and length, age, age at menarche, age at first birth, parity, tobacco smoking, alcohol consumption, and anthropometric and body composition variables were tested in factorial, fixed model, one-way ANOVA analyses, followed by Tukey–Kramer post-hoc tests.

Differences among the low ponderal index, moderate ponderal index, and high ponderal index groups in mean E2, mean luteal E2, and midcycle E2 were tested in factorial, two-way ANOVA analyses. Group division into low ponderal index, moderate ponderal index, and high ponderal index was used as one factor, and day of the menstrual cycle was used as the second factor (with 18 levels for mean E2, 9 levels for mean luteal E2, and 5 levels for midcycle E2). ANOVA was followed by contrast analyses; an alpha level of 0.0167 (with Bonferroni correction) was used to indicate statistical significance. To control for potential confounders, we performed covariance analyses with adult height as a covariate because the 3 ponderal index groups showed statistically significant differences in adult height. We also divided our subjects into tertiles of birth weight and into quartiles of birth weight and tested differences in indices of E2 among these groups in factorial, two-way ANOVA analyses. All P values were derived from two-sided statistical tests.

RESULTS

Baseline characteristics of the study subjects are presented in Table 1. The three groups characterized by different ponderal index showed significant variation in birth size characteristics (birth weight and birth length). The three groups also showed significant variation in adult body height: women from the low ponderal index group were taller as adults than women from the moderate ponderal index group ($P = 0.01$). Differences among three groups in all other variables were statistically insignificant.

Results of multiple regression analyses showed positive significant relationships between ponderal index and "mean nonaligned E2" ($P = 0.02$), "cycle day 0" ($P = 0.02$), and "cycle day −1" ($P = 0.03$), after controlling for potential confounders. Relationships with other E2 indices approached significance: "mean E2" ($P = 0.051$), "mean midcycle E2" ($P = 0.051$), and "mean luteal E2" ($P = 0.08$). None of the other independent factors (age, age at menarche, body weight, body height, cigarette smoking, or alcohol consumption) shows significant relationships with E2 indices (P values ranged from 0.10 to 0.99). Analyses with birth weight instead of ponderal index did not show a significant relationship between birth weight and E2 indices (P values ranged from 0.36 to 0.93). None of the potential confounders had a significant effect on E2 indices (P values from 0.14 to 0.99).

The regression-based results of the relationship between ponderal index and E2 indices were supported by the evidence of differences in hormonal profiles in "mean E2," "mean luteal E2," and "mid-cycle E2" among 3 groups characterized by differences in ponderal index. There was a significant variation among groups with low, moderate, and high ponderal index in mean E2 ($F_{2,2168} = 17.39$, $P = 0.0001$). The high ponderal index group had higher levels of mean E2 than the moderate ponderal index and low ponderal index groups ($P = 0.0001$ for both contrasts, Fig. 1). The difference in mean E2 between the low and moderate ponderal index groups was not statistically significant ($P = 0.16$).

Furthermore, ANOVA analyses with "mean luteal E2" and with "midcycle E2" as dependent variables showed a significant variation in E2 indices among the 3 tertiles of ponderal index ($F_{2,1057} = 16.31$, $P = 0.0001$ and $F_{2,620} = 3.22$, $P = 0.04$, respectively). The high ponderal index group had significantly higher luteal E2 levels than either the moderate or low ponderal index group ($P = 0.0001$ for both contrasts). The high ponderal index group also had higher midcycle E2 than the group with low ponderal index ($P = 0.014$). The three groups did not differ significantly in E2 concentration on the cycle day −1, on the day of ovulation (day 0), and did not show significant difference in the length of menstrual cycles (Table 2).

In a covariance analysis testing differences in mean E2 with adult height as a covariate,

*TABLE 1. Characteristics of all study subjects together and divided into groups with low, moderate, and high ponderal index (kg/m^3) at birth**

		Ponderal index			
		Low	Moderate	High	
	All women ($N = 145$)	Mean = 17.7 ($N = 46$)	Mean = 21.2 ($N = 48$)	Mean = 25.9 ($N = 51$)	P for trend[a]
Birth weight (g)	3315.6 (591.54)	3029.5 (635.5)	3363.5 (463.09)	3516.3 (575.48)	0.0001
Birth length (cm)	53.6 (3.77)	55.4 (3.42)	54.0 (2.56)	51.7 (4.12)	0.0001
Age (years)	29.2 (3.33)	28.9 (3.71)	28.8 (3.32)	29.8 (2.89)	0.32
Self-reported age of menarche (years)	13.2 (1.26)	13.4 (1.19)	13.1 (1.43)	13.3 (1.21)	0.50
Body weight (kg)	61.0 (9.8)	62.5 (10.39)	60.7 (11.32)	59.9 (7.31)	0.41
Body height (cm)	163.3 (6.33)	165.0 (6.77)	161.7 (5.38)	163.2 (6.39)	0.036
Body fat percentage	27.0 (7.27)	27.6 (7.44)	27.1 (8.01)	26.3 (6.27)	0.72
Body mass index (kg/m^2)	22.8 (3.33)	22.9 (3.24)	23.2 (4.16)	22.5 (2.4)	0.58
Age at first birth (years)	23.2 (3.12)	23.0 (3.07)	23.5 (3.39)	23.3 (2.99)	0.95
No. of children	0.88 (1.19)	0.9 (1.25)	1.1 (1.37)	0.7 (0.89)	0.24
Smoking (no. of cigarettes/day)	2.1 (4.96)	1.3 (3.28)	2.4 (5.46)	2.4 (5.69)	0.44
Drinking (alcohol units/week)	1.5 (1.26)	1.5 (1.45)	1.5 (1.34)	1.7 (1.34)	0.63

*Values given as means with standard deviations in parentheses.
[a]P values denote significance of variation among the 3 groups (from ANOVA analyses).

*TABLE 2. Estradiol indices and length of menstrual cycle in women from groups with low, moderate, and high ponderal index at birth**

	Ponderal index			
	Low	Moderate	High	*P* for trend[a]
Mean nonaligned E2 (pmol/L)	15.3 (7.62)	16.4 (7.41)	18.6 (8.02)	0.0001
Mean E2 (pmol/L)	16.5 (11.59)	17.3 (10.82)	19.6 (12.6)	0.0001
Mean mid-cycle E2 (pmol/L)	20.2 (14.67)	21.1 (13.12)	23.3 (15.5)	0.04
Mean luteal E2 (pmol/L)	15.7 (9.67)	16.7 (9.23)	19.7 (11.02)	0.0001
Day −1 (pmol/L)	32.1 (19.92)	32.4 (16.24)	35.7 (21.11)	0.61
Day 0 (pmol/L)	14.4 (10.62)	15.8 (7.63)	17.9 (10.68)	0.24
Length of the cycle in which saliva was sampled (days)	28.4 (3.84)	28.4 (3.58)	29.2 (3.54)	0.44

*Values given as means with standard deviations in parentheses.
[a]*P* values denote significance of variation among the 3 groups (from ANOVA analyses).

groups differing in ponderal index showed a significant variation in mean E2 ($F_{2,2114} = 27.37$, $P = 0.0001$), while adult height did not have a significant effect on E2 levels ($F_{1,2114} = 0.25$, $P = 0.62$).

Birth weight did not show a significant relationship with E2 indices in multiple regression analyses with the same potential confounders as in the multiple regressions with ponderal index described above (*P* values ranging from 0.36 to 0.93 for different E2 indices). Lack of a significant relationship was confirmed by ANOVA analysis that did not show significant differences in mean E2 among tertiles of birth weight ($F_{2,2399} = 2.05$, $P = 0.13$) and by analysis of covariance with adult height as the covariate ($F_{2,2399} = 2.11$, $P = 0.12$). However, when women were divided into quartiles of birth weight, ANOVA analysis showed a significant difference in mean E2 ($F_{3,2381} = 8.19$, $P = 0.0001$): women from the lowest birth weight quartile (first quartile) had lower E2 than women from any of the three other quartiles ($P = 0.0004$, $P = 0.003$, and $P = 0.0001$ for significance of differences with the second, third, and fourth quartile of birth weight, respectively; Table 3).

DISCUSSION

The results of our study suggest that size at birth is one of the factors underlying variance in levels of estradiol among reproductive age women. Further, these results suggest a possible physiological mechanism for the association between an individual's characteristics at birth and her subsequent risk of breast cancer. Women with higher ponderal index had higher levels of E2 in menstrual cycles. High lifetime levels of estrogens are hypothesized to be a major risk factor for breast and other hormone-dependent cancers in women (Pike et al., 1993). Indeed, exposure to high levels of estrogens may begin in utero; studies show that high levels of pregnancy estriol are positively correlated with size at birth (Mucci et al., 2003).

In our study, levels of estradiol were measured in samples of saliva collected daily for an entire menstrual cycle for each woman. Salivary levels reflect the unbound, biologically active fraction of steroids, and when they are collected daily, salivary samples allow for the precise assessment of steroid hormone levels. Data on birth weight and birth length were obtained from written medical records and are thus free from recollection bias. Anthropometric measurements for all adult women were made by the same person, and consequently were not subject to inter-observer error.

In our study, birth weight did not show a significant linear relationship with estradiol

TABLE 3. Mean birth weight and estradiol levels in women from birth weight quartiles

	1st quartile ($N = 34$)	2nd quartile ($N = 35$)	3rd quartile ($N = 32$)	4th quartile ($N = 34$)
Mean birth weight (g)	2599 (422.6)[a]	3206 (88.2)	3530 (77.1)	3983 (252.1)
Range of birth weight (g)	1300–3000	3010–3360	3400–3670	3700–4800
Mean E2 (pmol/L)	16.4 (10.51)[b]	19.3 (12.88)	18.2 (12.32)	18.3 (11.3)

[a]Standard deviations are given in parentheses.
[b]Mean E2 for the 1st quartile was lower in comparison to all three remaining quartiles ($P < 0.003$).

levels. Only women from the lowest quartile of birth weight (1300–3000 g) had reduced estradiol levels in comparison to women with higher birth weight (Table 3). Ponderal index may, however, be a better indicator of newborn nutritional status than birth weight, in the same way that BMI reflects adult nutritional status better than adult body weight. Maternal weight and BMI in pregnancy are strongly linearly associated with baby's ponderal index at birth (Forsen et al., 1997), suggesting that ponderal index reflects maternal nutritional status. In addition, animal studies show that maternal undernutrition in late gestation may influence the offspring's body proportions without affecting birth weight (Barker, 1997). Therefore, in epidemiological research investigating relationships between early environment and subsequent risk of breast cancer, the use of ponderal index, in addition to birth weight, may help resolve the conflicting results of different studies.

It has been postulated that the observed relationships between indices of fetal condition and breast cancer may be mediated by (1) the maternal hormonal environment directly affecting the fetal breast (Trichopoulos, 1990) or (2) the maternal environment influencing the development and programming of the fetal neuroendocrine axis (Davies and Norman, 2002). Our data on variation in estradiol levels in relation to differences in ponderal index support the latter hypothesis, although both mechanisms may be important.

In addition to variation in estradiol levels, other aspects of female reproductive function also seem to be influenced by the fetal environment, further supporting the hypothesis that early programming has important effects on a woman's reproductive physiology (Davies and Norman, 2002). Girls born small for gestational age show, as adolescents, reduced uterine and ovarian size, reduced rates of ovulation, and ovarian hyporesponsiveness to follicle-stimulating hormone (Ibanez et al., 2000a, 200b, 2002). Birth characteristics have been implicated as factors partially determining age at menarche and at menopause (Adair, 2001; Cresswell et al., 1997). Early menarche has been shown to be related to a more rapid onset of ovulatory cycles and higher levels of ovarian steroids produced during cycles for several years after the menarche (Apter, 1996).

Birth weight and ponderal index probably represent nonmodifiable risk factors for breast cancer. Higher birth weight has been linked to increased risk of cancer, but also to reduced risks of cardiovascular diseases and diabetes (Barker, 1997). However, some studies have found a U-shaped association between birth measurements and risk factors for heart disease (Barker, 1995), suggesting that very high birth weight may not be advantageous. Size at birth is linked to maternal nutrition during pregnancy and also to energy status before pregnancy (Brown et al., 1996; Neggers et al., 1997). While adequate maternal nutrition is important, pregnant women, like the rest of the population in modern, industrial societies, may have excessive energy intake. Such high intake during pregnancy combined with high maternal prepregnancy BMI may be leading to newborns so large that they are outside the "normal" healthy range established during the evolution of the human species. Secular trends in increasing birth size and increasing proportion of large for gestational age births have recently been documented for several populations (Surkan et al., 2004; Wen et al., 2003).

Finally, an interaction among characteristics resulting from fetal programming and from adult lifestyle may be important in determining the relationship between size at birth and risk of breast cancer. In some countries, low birth weight is not related to an increased risk of atherosclerosis, probably due to adult lifestyle influences (Scrimshaw, 1997). Similarly, it is possible that an increased risk of breast cancer associated with high birth weight can also be reduced by an adult lifestyle characterized by high physical activity and lack of weight gain. Such a lifestyle may lead to low lifetime levels of estradiol both in pre- and postmenopausal periods, thereby contributing to a reduced risk of breast cancer.

ACKNOWLEDGMENTS

We are grateful to the women who participated in this study, to students of the Faculty of Public Health, Jagiellonian University, who worked as research assistants, to Dr. Mary O'Rourke from Harvard University, Rev. Józef Puchata of the Jurków parish in Poland, Miraculum Cosmetics, and Yves Rocher Poland. This study was supported by Polish State Committee for

Scientific Research and Norwegian Cancer Society.

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