Published in final edited form as:

Cancer Causes Control. 2011 April ; 22(4): 611–621. doi:10.1007/s10552-011-9734-7.

Birth characteristics and female sex hormone concentrations during adolescence: results from the Dietary Intervention Study in Children

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Abstract

Background—Birth characteristics and adult hormone concentrations influence breast cancer risk, but little is known about the influence of birth characteristics on hormone concentrations, particularly during adolescence.

Methods—We evaluated the association of birth characteristics (birth weight, birth length, and gestational age) with serum sex hormone concentrations during late childhood and adolescence in 278 female participants of the Dietary Intervention Study in Children. Repeated measures analysis of variance models were used to assess the relationships of birth characteristics and serum estrogens and androgens at five different time points over a mean period of 7 years.

Results—In analyses that did not take into account time from blood draw until menarche, birth weight was inversely associated with pre-menarche concentrations of estradiol, estrone sulfate, androstenedione, testosterone, and dehydroepiandrosterone sulfate (DHEAS). In the post-menarche analyses, birth weight was not significantly associated with concentration of any of the hormones under investigation. Birth length and gestational age were not associated with hormone concentrations before or after menarche.

Conclusion—Birth weight is inversely associated with sex hormone concentrations before menarche in the model unadjusted for time from blood draw until menarche.

Impact—The in utero environment has long-term influences on the hormonal milieu, which could potentially contribute to breast cancer risk.

Keywords

Birth weight; Sex steroid hormones; Breast cancer risk factors; Adolescence; Puberty

Introduction

A recent meta-analysis of size at birth and breast cancer risk concluded that both birth weight and birth length are positively associated with adult breast cancer risk, with no significant difference in the association by menopausal status at diagnosis [1]. The biologic mechanism(s) behind these associations are unclear, but may be related to pre-natal programming of neuroendocrine systems [2]. The prenatal period and puberty are critical times for maturation of the hypothalamic pituitary adrenal (HPA) and hypothalamic pituitary ovarian (HPO) axes, which via complex feedback loops maintain the concentrations of estrogens, progesterone, testosterone androstenedione, and dehydroepiandrosterone sulfate (DHEAS) in the normal range [3]. A substantial body of epidemiological, clinical, and experimental research suggests that adult hormone concentrations play a major role in the etiology of female breast cancer. Higher circulating estrogens and androgens as well as lower sex hormone-binding globulin (SHBG) concentrations were associated with increased risk for post-menopausal breast cancer in a pooled analysis of nine prospective studies [4]. Elevated serum testosterone also has been associated with increased breast cancer risk in pre-menopausal women [5, 6]. Cyclic variation of estrogens and progesterone complicates analyses of associations of pre-menopausal levels of these hormones with breast cancer risk, but results from a large, prospective nested case-control study with blood samples timed within the menstrual cycle suggest that elevated circulating estrogens also may be important in the etiology of pre-menopausal breast cancer [5].

Given that breast tissue is largely undifferentiated prior to age 20 years [7] and hormone levels increase during puberty, adolescence could be an important period for hormonal influence on future breast cancer risk. Lower birth weight is associated with earlier age at menarche in the Dietary Intervention Study in Children (DISC) [8], as well as other studies [9–13]. In this investigation, we hypothesize that smaller birth size is associated with higher sex steroid hormone concentrations in late childhood and adolescence. Specifically, we explore the association of birth weight, birth length, and gestational age with serum estrogens, progesterone, androgens, and SHBG concentrations before and after menarche among female participants in the Hormone Ancillary Study (HAS) to the DISC.

Materials and methods

We combined data from female participants in the original DISC/HAS (conducted 1988–1997) with additional birth characteristic information collected from the DISC Follow-up Study (conducted 2006–2008, hereafter referred to as DISC06). Briefly, the HAS was conducted ancillary to DISC, which was a two-armed, multi-center, randomized clinical trial sponsored by the National Heart Lung and Blood Institute (NHLBI). The purpose of DISC was to assess the efficacy of a reduced fat dietary intervention on low-density lipoprotein cholesterol (LDL), and the safety of the intervention to promote growth and development. The HAS evaluated the effect of the intervention on serum sex hormone levels. DISC was conducted at 6 clinical centers, and details about the study have been published [14]. Major inclusion criteria included baseline age of 8–10 years, serum LDL cholesterol level in the 80–90th percentiles, no major illnesses, height greater than or equal to the 5th percentile for age and weight-for-height in the 5–90th percentiles, and Tanner Stage 1 for breast and pubic hair development. Girls were not eligible to participate in the HAS if they were pregnant or had used oral contraceptives within 3 months of blood collection, if they were

post-menarcheal and had missing data on the date they started their next menses after blood collection, or if their next menses started more than 33 days after blood collection. The mean duration in the DISC for participants in the present analysis was 7.1 years. The purpose of the DISC06 was to evaluate female DISC participants in early adulthood (ages 25–29) for potential effects of the DISC intervention during puberty on biomarkers associated with breast cancer risk [15]. Institutional Review Boards at all participating centers approved both DISC protocols, and an NHLBI-appointed independent data and safety monitoring committee provided oversight for the original DISC investigation.

Data collection

Data for the original DISC were collected prior to randomization and annually thereafter by trained staff who were blinded to treatment assignment. Demographic characteristics, medical history, physical activity, and use of medications were obtained via self-report with parental assistance where necessary. Dietary intake was assessed via three 24-h dietary recalls at each visit. Measures of weight, height, and body mass index (BMI: weight in kg/height in m²) were obtained using standardized techniques previously described [14]. Onset of menses in DISC was reported to the nearest day and ascertained annually until menarche was reached or the study concluded. There were $n = 34$ individuals for whom age at menarche was not reported in the original DISC investigation, but who did report age at menarche in DISC06. Our final sample for menarche data was comprised of 250 individuals from the original data collection plus 28 individuals who reported age at menarche only in the follow-up study and had data on hormones and covariates (total $n = 278$). Birth weight was recorded to the nearest ounce or gram as part of the mothers'/guardians' questionnaire for the year 3 visit of the original DISC study. A total of $n = 203$ (67.4%) participants had a reported birth weight as part of the year 3 visit, but it was unknown whether the report was made by the participants' mothers or another adult accompanying the child to the visit. To capture more complete birth characteristics, data, birth weight, in addition to birth length and gestational age, were obtained as part of DISC06. The young women were sent a birth characteristics questionnaire by mail prior to their clinic visit and asked to consult their birth certificates, records, and family members in order to provide an accurate report. The questionnaire ascertained birth weight (pounds, ounces), birth length (to the nearest tenth of an inch), gestational age (in weeks) and whether the pregnancy was full term (specified as ≥ 37 weeks). Two hundred and sixty-women participated in the DISC06, and response rates for the birth characteristics were high (99.6% for birth weight, 94.2% for birth length, 75.0% for gestational age in weeks, and 99.6% for whether the birth was term (Y/N)). Ponderal index was calculated: $(100 \times \{(\text{weight in grams})/(\text{length in centimeters})^3\})$. Women could report one or more source(s) for birth characteristics: 87% ($n = 226$) reported asking their mothers, 57% ($n = 149$) reported themselves as a source of information, 14% ($n = 37$) reported using a baby book, 14% ($n = 37$) reported consulting other people or other records, and 9% ($n = 24$) reported consulting their birth certificate. In total, birth weight was available for $n = 282$ girls comprised of $n = 259$ with birth weights collected at the follow-up visit and $n = 23$ who reported birth weight only in the original DISC study. Of these, $n = 278$ had complete data on covariates. The Pearson correlation coefficient for birth weight among the 180 women with a recorded birth weight during the original DISC and the DISC06 follow-up was 0.87 ($p < 0.0001$, mean difference = -5.65 g, 95% confidence interval (CI): -42.39 to 31.07 g).

During DISC, a single blood sample was collected by venipuncture in the morning after an overnight fast at baseline and at the year 1, year 3, year 5, and the last visits (approximately 7 years after randomization). The blood sample was kept at room temperature for at least 45 min to allow complete clotting, and serum was separated by centrifugation. Serum was then aliquoted and stored in glass vials at -80°C until it was analyzed for hormone, lipid, and

micronutrient levels. Blood collections were not timed to the menstrual cycles of the post-menarcheal girls. However, the post-menarcheal girls kept menstrual cycle calendars for 6 weeks before and 6 weeks after their blood collections, and we identified the day of the menstrual cycle at blood collection using days until onset of next menses as recorded on their menstrual cycle calendars.

Hormone assays were performed by Esoterix Endocrinology, Inc. (Calabasas Hills, CA). Steroid hormones were measured by radioimmunoassay, and SHBG was measured by an immunoradiometric assay [16, 17]. The concentration of non-SHBG-bound estradiol was calculated as the product of the total estradiol concentration and the percent non-SHBG-bound estradiol, which was measured by ammonium sulfate precipitation [17]. To monitor the quality of hormone assays, masked quality control samples were included with participant samples in each batch. These samples were aliquots from three serum quality control pools that were created by serially diluting serum from adults with charcoal stripped serum to cover the range of steroid concentrations expected in participant samples. Within-visit coefficients of variation (CV) estimated from quality control samples were 8–29% for estradiol, 12–31% for estrone, 12–17% for estrone sulfate, 4–10% for progesterone, and 15% for SHBG. Low concentrations of hormones in some quality control samples may have contributed to the higher CVs observed for some hormones. For example, the mean concentrations of estradiol in samples from the three quality control pools were 0.9, 2.8, and 11.3 ng/dl, and their corresponding within-visit CVs were 29, 11, and 8% [18].

Statistical analysis

Statistical analyses were performed using SAS software (SAS System for Windows, version 9.1; SAS Institute, Cary, NC). Because few participants were of clinical low birth weight (<2,500 g) or high birth weight (≥4,000 g), we sought an alternate approach to categorize birth size. Birth weight, gestational age, and birth length were categorized into one of three categories: <1 standard deviation (SD) below the sample mean ('lower' or 'early'), within ±1 SD of the sample mean ('average'), or >1 SD above the sample mean ('higher' or 'late'). BMI-for-age percentile, weight-for-age percentile, and height-for-age percentile were calculated using the Centers for Disease Control SAS Program for Growth Charts [19]. One-way ANOVAs were used to compare differences in mean baseline BMI-for-age percentile, weight-for-age percentile, height-for-age percentile, total daily energy intake, and age at menarche between low, average, and high birth weight groups. Chi-square tests were used to compare differences in birth characteristics by treatment group. Only participants with complete data on variables of interest ($n = 278$) were included in analyses.

Repeated measures ANOVA (also called mixed linear regression) models were used to calculate the mean hormone concentrations at baseline and during follow-up in the original DISC study according to category of birth characteristic after controlling for potential covariates described in the following section. Differences between the mean values of each category were computed using the least squares means of fixed effects. Mixed linear regression models were also used to examine birth characteristics as continuous variables. Serum hormone data were $\log_e$ transformed before analysis to improve normality, but reverse-transformed to compute geometric means and 95% confidence intervals (95% CI). Separate models were used to fit pre- and post-menarcheal samples, with additional separate models for the follicular and luteal phases for estradiol, non-SHBG-bound estradiol, estrone, estrone sulfate, and progesterone. Progesterone was only measured for the post-menarcheal girls. Post-menarche serum samples collected <15 days before the next menses were classified as luteal, and samples collected 15 through 33 days before or on the day of onset of the next menses were classified as follicular. Post-menarcheal girls whose next menses started more than 33 days after blood collection were not included in the analyses. Androgens and SHBG, unlike estrogens and progesterone, do not vary substantially over the

course of the menstrual cycle and analyses of these hormonal biomarkers were conducted without regard to menstrual cycle day. Thus, four separate regression models were used: pre-menarcheal samples for all hormones and SHBG, post-menarcheal samples for androgens and SHBG, and separate luteal and follicular phase samples for the estrogens and progesterone. All models were adjusted for two sets of covariates. The first set included DISC clinic visit number, treatment group, age, and for the analyses of the estrogens and progesterone among the post-menarcheal girls, and a categorical variable for day of the menstrual cycle when blood was collected. The second set adjusted for the aforementioned variables plus years until menarche for the pre-menarche samples and years since menarche for the post-menarche samples. Additional covariates, including body mass index and physical activity, were investigated but did not materially alter the effect of birth weight, birth length, or gestational age on hormone concentrations and were not included in the final model. Interaction between category of birth weight (lower birth weight, average birth weight, and higher birth weight) and three BMI-for-age percentile categories (≤ 50 th percentile, 50–85th percentile, ≥ 85 th percentile) at study baseline was evaluated by including cross-product terms in multivariate models.

Results

Baseline characteristics

A total of 278 (97%) of the 286 girls who participated in the DISC-HAS had a documented birth weight and age at menarche. The mean birth weight was 3,411 g (SD = 496, range 1,899–5,103). Twenty-nine girls (10.4%) reported clinical low birth weight ($\leq 2,500$ g at birth) and twenty-seven girls (9.7%) reported weighing $\geq 4,000$ g at birth. Birth length was available for $n = 244$ girls (mean = 51.14 cm, SD = 2.79, range 40.64–57.15), and gestational age was available for $n = 195$ girls (mean = 38.71 weeks, SD = 2.27, range 24.0–43.0). A total of 19 girls (9.74%) reported a gestational age of < 37 weeks. Baseline characteristics of the participants according to category of birth weight are presented in Table 1. There were no significant differences in unadjusted BMI-for-age percentile, height-for-age percentile, weight-for-age percentile, or total daily energy intake across categories of birth weight. Mean age at menarche was significantly older for girls in the high birth weight category compared to girls in the low birth weight category.

Hormone concentrations in pre-menarcheal samples

The median duration until menarche for girls at the time of the pre-menarche blood collections was 3.55 years (range 0.7–8.5 years). Interactions between birth weight and category of BMI-for-age percentile on concentration of pre-menarche sex steroid hormones were not significant (data not shown). Birth weight was inversely associated with estradiol concentrations when years until menarche was not included as a covariate (Table 2). Lower birth weight girls' mean estradiol concentration was 1.91 ng/dl (95% CI = 1.41, 2.60), which was significantly higher than that for average birth weight (1.42 ng/dl; 95% CI = 1.13, 1.77) and higher birth weight (1.38 ng/dl; 95% CI = 1.01, 1.90) girls. Patterns of decreasing concentration with increasing birth weight categories were similar for non-SHBG-bound estradiol. Moreover, trends of decreasing total and non-SHBG-bound estradiol with increasing birth weight modeled as a continuous variable were statistically significant. Estrone sulfate, androstenedione, testosterone, and DHEAS concentrations also decreased across increasing categories of birth weight; although differences among categories were not significant, trends based on continuous birth weight were statistically significant (Table 2). After adjustment for years until menarche, birth weight was no longer associated with pre-menarcheal concentrations of any of the hormones measured. Birth length and gestational age were not associated with any of the hormones or SHBG concentrations regardless of adjustment for years until menarche (data not shown). Ponderal index was examined, but

was not significantly associated with any of the hormones or SHBG concentrations (data not shown).

Hormone concentrations in post-menarcheal samples

The median duration since menarche at the time of blood collection was 1.3 years (range 0.01–5.4 years). Interactions between birth weight and category of BMI-for-age percentile on concentration of post-menarche sex steroid hormones were not significant (data not shown). After menarche, none of the hormones measured were statistically significantly associated with birth weight (Table 3). Similar to the pre-menarche analysis, neither birth length or gestational age, nor ponderal index was associated with any of the hormones or SHBG concentrations regardless of adjustment for years until menarche (data not shown).

Discussion

Our study sought to investigate whether birth characteristics are associated with sex hormone concentrations during late childhood and adolescence. This is the first published study with longitudinal hormone measurements beginning prior to puberty and continuing through adolescence to investigate these relationships. We detected significant inverse associations of birth weight with pre-menarcheal concentrations of serum total and non-SHBG-bound estradiol, estrone sulfate, androstenedione, testosterone, and DHEAS. Post-menarcheal concentrations of DHEAS were higher among lower birth weight girls compared to those who were average birth weight, but overall, there was no association of birthweight with DHEAS concentration in the post-menarche period. The other androgens and estrogens did not differ across birth weight categories among the post-menarche samples. Gestational age and birth length were not associated with any of the sex hormones or SHBG either before or after menarche.

Given that both higher birth weight and higher adult circulating concentrations of hormones are associated with increased risk of breast cancer [4, 5, 20], our results indicating that lower birth weight is associated with higher hormone concentrations prior to menarche may seem initially counterintuitive. However, breast tissue is in a dynamic state during adolescence [7], and it is possible that hormone exposure could have differential effects on breast cancer risk over the life course. Indeed, several animal studies support this hypothesis. Rat models show that pre-pubertal exposure to genistein, a weak estrogenic component in soy products, reduces the number of the highly proliferative terminal end buds in breast tissue and increases the density of the more highly differentiated lobulo-alveolar units [21, 22]. Furthermore, pre-pubertal exposure to either genistein or estradiol reduces the risk of carcinogen induced mammary tumors, likely due to changes in mammary gland morphology. In addition, mRNA expression of the *BRCA1* tumor suppressor gene is upregulated in mammary glands of rats exposed to either genistein or estradiol prepubertally [23]. Although no human work has examined exposure to estrogen or other hormones in the pre-pubertal period with later risk of breast cancer, child and adolescent intake of soy foods has been inversely associated with later risk of breast cancer, while the relationship between adult intake of soy foods and breast cancer risk is less clear [24–27].

Serum estradiol concentration progressively increases during early puberty, and elevation of estradiol to a high enough concentration stimulates a surge of luteinizing hormone to prompt menstruation [28]. By controlling for time from blood collection until menarche in a subset of our analyses, we attempted to control for the natural increase expected in estrogens when menarche is nearing. Lower birth weight was associated with increased estradiol concentrations in the pre-pubertal period in the analyses unadjusted for time until menarche, but not in those adjusted for time until menarche. Thus, we speculate that the birth weight-associated increase in estradiol concentration stimulates the hormonal cascade to prompt

menarche at an earlier age. Results from our previous research documented a significant positive association between birth weight and age at menarche in the DISC girls [8]. Together with the present study, these results provide a framework, suggesting that lower birth weight is associated with increased hormone concentrations in the pre-menarche period; in turn, these elevated hormones may protect pre-pubertal breast tissue, despite prompting an earlier age at menarche. Although speculative, this provides a unifying hypothesis for how lower birth weight may be associated with both earlier menarche and reduced breast cancer risk. Additional research is needed to address this hypothesis directly.

The present study is unique due to the multiple hormone measurements over time, but our results are in agreement with those from cross-sectional investigations and cohorts of shorter duration. We documented a decreasing trend in concentration of the pre-menarcheal adrenal hormone androstenedione and a higher DHEAS concentration in post-menarcheal girls who were lower birth weight in the analyses not adjusted for years until/since menarche. Similar to our findings, three cross-sectional studies have documented higher concentrations of DHEAS during childhood and adolescence among individuals born small-for-gestational age (SGA) compared to individuals born average-for-gestational (AGA) [29–31], and one cross-sectional study of girls with a mixture of birth sizes documented an inverse association of birth weight and adolescent DHEAS concentration [32]. A cohort study of pre-pubarcheal boys and girls born SGA was also complementary to our findings and indicated increased concentration of circulating DHEAS and decreased concentration of circulating SHBG compared with AGA peers between 6 and 8 years of age. Evidence of a continuous association between lower birth weight and higher childhood DHEAS and androstenedione concentrations throughout the range of normal birth weights in both boys and girls has also been documented [33], but results indicating no association of birth weight with DHEAS have also been published [34]. Less evidence is available to show an effect of the intra-uterine environment on programming of the HPO axis. Our study found significant inverse associations of birth weight with pre-menarcheal concentrations of serum total and non-SHBG-bound estradiol, estrone sulfate. Similar to our findings, a cross-sectional study of healthy 8-year-old pre-pubertal females reported a negative correlation between birth weight and estradiol [34]. A study of young adult women (aged 24–36 years) detected the direction of the relationship between birth size and estradiol to be opposite of what we found. In that study, a positive association of ponderal index at birth (a measure of body size, calculated as $\text{birth weight/birth length}^3 \times 100$) was detected with salivary estradiol over the course of one menstrual cycle [35]. Although substantial differences in study design exist between the previous study and our investigation, it illuminates again the important possibility that birth size may have different associations with hormones at various stages in the lifecourse. Differential associations birth weight and hormones over the lifecourse and ultimately, the association of hormone concentrations and risk of breast cancer at various life stages (e.g., pre-pubertal, pubertal) is an area in need of more research.

We did not see an association of birth length or gestational age with concentration of any of the measured hormones or SHBG, although association of these birth characteristics with risk of breast cancer is also less consistent than that of birth weight [20]. Furthermore, fewer DISC participants had data on birth length and gestational age compared to birth weight, and we may not have been adequately powered to detect an association.

The present research has some limitations. The study population was comprised of girls with elevated serum LDL cholesterol levels and who were between the 5th and 95th weight-for-height percentiles. As such, our results may not be generalizable to the greater population. Birth characteristics were self-reported and may have been subject to error. However, most DISC participants asked their mothers for information on their birth characteristics and maternal report of birth characteristics are highly correlated with birth characteristics in the

medical record, although birth weight is more accurately recalled than other birth characteristics [20, 36, 37]. This may be one reason why we detected an association with birth weight and certain hormones but not birth length or gestational age. Our blood collections were not timed with the menstrual cycle, and categorization of menstrual cycle phase was dependent on the accuracy of the girls' daily menstrual calendars. It is possible that misreporting could have biased our post-menarche results toward the null. In addition, we lack information on concentration of non-sex steroid hormones involved in pubertal development, including the adipose hormone leptin, the gut hormone ghrelin, as well as the peptide kisspeptin that was recently identified as a player in the signaling of gonadotropin-release hormone release during puberty [38]. Finally, radioimmunoassays, rather than mass spectrometry, were used in DISC/HAS. However, a validation study comparing radioimmunoassay to mass spectrometry in DISC/HAS indicated that the two methods produced comparable estimates [16].

The present investigation has numerous strengths that outweigh its limitations. To the best of our knowledge, it is the first published study to investigate the association of birth size with longitudinal hormone measurements prior to puberty and continuing through adolescence. Serum hormone assays were performed using highly specific radioimmunoassays, and estradiol, estrone, estrone sulfate, and testosterone radioimmunoassay were preceded by a chromatographic purification step. Additional strengths include that menstrual cycles were recorded in a diary and not dependent on recall, phase of the menstrual cycle was controlled for and we adjusted for days until the beginning of next menstrual cycle, and multiple hormone measurements were available for most participants.

In conclusion, birth weight was inversely associated with pre-menarche estradiol, estrone sulfate, androstenedione, and testosterone. Further research is needed to confirm these relationships and explore how they relate to breast cancer risk.

Acknowledgments

The work described was supported by Grant Number R01CA104670 from the National Cancer Institute.

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Table 1

Characteristics of girls who participated in the dietary intervention study/hormone ancillary study according to birth weight

	Birth weight group ¹ (range in grams)			<i>p</i> value [‡]
	Lower birth weight (<i>n</i> = 43)	Average birth weight (<i>n</i> = 201)	Higher birth weight (<i>n</i> = 34)	
Birth weight, g, mean (SD)	2,630 (238)	3,441 (272)	4,222 (261)	
Range	1,899–2,892	2,920–3,884	3,912–5,103	
Treatment group				
Intervention (<i>n</i>)	18	99	19	
Usual care (<i>n</i>)	25	102	15	0.47 [‡]
BMI-for-age percentile at study baseline ² , mean (SD)	50.41 (28.65)	57.52 (27.41)	60.13 (28.68)	0.28 ^a
				0.87 ^b
				0.28 ^c
Height-for-age percentile at study baseline, mean (SD)	44.01 (26.89)	49.62 (27.12)	49.87 (29.23)	0.44 ^a
				0.99 ^b
				0.62 ^c
Weight-for-age percentile at study baseline, mean (SD)	46.03 (27.67)	54.02 (28.38)	56.09 (11.60)	0.21 ^a
				0.92 ^b
				0.27 ^c
Total daily energy intake at baseline, mean (SD)	1,618 (520)	1,683 (479)	1,689 (380)	0.71 ^a
				0.99 ^b
				0.81 ^c
Age at menarche, years, mean (SD)	12.57 (1.09)	12.88 (1.18)	13.37 (1.32)	0.29 ^a
				0.07 ^b
				0.01 ^c
Race (<i>n</i>)				
White	35	172	29	
Black	4	8	3	
Asian	2	9	0	
Missing	2	12	2	

[†] *p* value from ANOVA unless noted otherwise

[‡] *p* value from χ^2 test

¹ Group 1: birth weight <1 standard deviation (SD) below sample mean; Group 2: within $\pm$ 1 SD of sample mean; Group 3: birth weight >1 SD above sample mean

² Mean age at baseline = 9.14 years, range 8.02–10.35 years

Table 2

Mean pre-menarche serum hormones and SHBG concentrations in DISC girls according to (a) birth weight ($n = 278$) (b) birth weight, adjusted for years until menarche ($n = 278$)

	<i>n</i> samples (max samples per individual)	Lower birth weight ($\leq 2,892$ g) Mean (95% CI)	Average birth weight (2,920–3,884 g) Mean (95% CI)	Higher birth weight ($\geq 3,912$ g) Mean (95% CI)	<i>p</i> value
<i>(a)</i>					
Estradiol, ng/dl [†]	451	1.91 (1.41, 2.60) ^{a,b}	1.42 (1.13, 1.77) ^a	1.38 (1.01, 1.90) ^b	0.04 ^I
	5				0.02 ²
Non-SHBG-bound estradiol, ng/dl [†]	388	0.98 (0.65, 1.49) ^{a,b}	0.73 (0.53, 1.01) ^a	0.64 (0.42, 0.97) ^b	0.05 ^I
	4				< 0.01 ²
Estrone, ng/dl [†]	451	1.71 (1.40, 2.09)	1.58 (1.37, 1.82)	1.58 (1.29, 1.93)	0.59 ^I
	5				0.26 ²
Estrone sulfate, ng/dl [†]	355	49.60 (38.17, 64.45)	42.52 (34.91, 51.80)	40.91 (31.42, 53.27)	0.23 ^I
	4				0.04 ²
Androstenedione, ng/dl [†]	444	67.10 (54.88, 82.05)	57.37 (49.83, 66.06)	55.11 (44.74, 67.89)	0.13 ^I
	5				0.01 ²
Testosterone, ng/dl [†]	381	15.44 (11.02, 21.64)	13.73 (10.55, 17.87)	13.06 (9.26, 18.43)	0.62 ^I
	4				0.05 ²
DHEAS, ng/dl [†]	453	47.12 (36.68, 53.35)	43.77 (37.04, 45.82)	40.84 (31.46, 51.55)	0.52 ^I
	5				< 0.05 ²
SHBG, nmol/dl [†]	453	91.55 (74.64, 112.29)	90.77 (79.16, 104.07)	105.35 (85.14, 130.36)	0.28 ^I
	4				0.42 ²
<i>(b)</i>					
Estradiol, ng/dl [†]	451	1.69 (1.30, 2.19)	1.39 (1.15, 1.69)	1.50 (1.15, 1.96)	0.16 ^I
	5				0.24 ²
Non-SHBG-bound estradiol, ng/dl [†]	388	0.85 (0.70, 1.04)	0.67 (0.64, 0.76)	0.73 (0.60, 0.90)	0.20 ^I
	4				0.10 ²
Estrone, ng/dl [†]	451	1.62 (1.36, 1.93)	1.59 (1.40, 1.80)	1.68 (1.41, 2.01)	0.71 ^I

	<i>n</i> samples (max samples per individual)	Lower birth weight (≤2,892 g) Mean (95% CI)	Average birth weight (2,920–3,884 g) Mean (95% CI)	Higher birth weight (≥3,912 g) Mean (95% CI)	<i>p</i> value
Estrone sulfate, ng/dl [‡]	5				0.97 ²
	355	42.50 (33.85, 53.35)	38.59 (32.50, 45.82)	41.07 (32.71, 51.55)	0.42 ¹
	4				0.34 ²
Androstenedione, ng/dl [‡]	444	59.20 (49.49, 70.82)	53.63 (47.28, 60.84)	55.71 (46.36, 66.94)	0.38 ¹
	5				0.15 ²
Testosterone, ng/dl [‡]	381	13.02 (9.70, 17.47)	12.55 (9.97, 15.78)	13.14 (9.76, 17.70)	0.86 ¹
	4				0.32 ²
DHEAS, ng/dl [‡]	453	42.41 (33.23, 54.14)	40.91 (34.74, 48.16)	41.01 (31.93, 52.68)	0.94 ¹
	5				0.20 ²
SHBG, nmol/dl [‡]	453	96.80 (78.92, 118.72)	94.13 (82.08, 107.94)	105.28 (85.37, 129.83)	0.48 ¹
	4				0.74 ²

SD standard deviation, *CI* Confidence interval, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate

^{a,b}

Items in the same row marked with the same letter differ at $p \leq 0.05$

¹

p value for categorical birth weight;

²

p value for continuous birth weight

[‡]

Geometric means and 95% CI adjusted for years until menarche, visit number, treatment group, and age

[‡]

Geometric means and 95% CI adjusted for years until menarche, visit number, treatment group, age, and years until menarche

Table 3

Mean post-menarche hormone and SHBG concentrations in DISC girls according to (a) birth weight, (b) birth weight, adjusted for years since menarche

	<i>n</i> samples <i>n</i> individuals (max samples per individual)	Lower birth weight ≤2,892 g Mean (95% CI)	Average birth weight 2,920–3,884 g Mean (95% CI)	Higher birth weight ≥3,912 g Mean (95% CI)	<i>p</i> value
(a)					
Combined luteal and follicular phase					
Androstenedione, ng/dl [‡]	346	139.17 (124.70, 155.31)	126.65 (119.41, 134.33)	122.90 (108.30, 139.49)	0.21 [‡]
	205				0.08 ²
	3				
Testosterone, ng/dl [‡]	343	31.20 (27.01, 36.05)	28.25 (26.19, 30.47)	27.58 (23.43, 32.46)	0.38 [‡]
	205				0.20 ²
	3				
DHEAS, lg/dl [‡]	347	125.19 (107.07, 146.35) ^a	104.06 (96.13, 112.65) ^a	103.60 (86.7, 123.80)	0.08 [‡]
	205				0.17 ²
	3				
SHBG, nmol/dl [‡]	348	61.76 (52.63, 72.49)	62.82 (57.95, 68.12)	66.84 (55.72, 80.17)	0.78 [‡]
	205				0.42 ²
	3				
Luteal phase					
Estradiol, ng/dl [‡]	162	10.13 (7.56, 13.38)	10.05 (8.59, 11.77)	10.66 (7.64, 14.88)	0.95 [‡]
	127				0.72 ²
	3				
Non-SHBG-bound estradiol, ng/dl [‡]	162	5.10 (3.87, 6.70)	5.06 (4.36, 5.87)	5.52 (4.04, 7.55)	0.81 [‡]
	127				0.63 ²
	3				
Estrone, ng/dl [‡]	162	5.50 (4.37, 6.94)	5.22 (4.62, 5.91)	5.68 (4.37, 7.38)	0.79 [‡]
	127				0.92 ²
	3				
Estrone sulfate, ng/dl [‡]	165	130.86 (96.15, 178.11)	137.04 (116.37, 161.40)	157.51 (112.98, 219.60)	0.68 [‡]

	<i>n</i> samples <i>n</i> individuals (max samples per individual)	Lower birth weight ≤2,892 g Mean (95% CI)	Average birth weight 2,920–3,884 g Mean (95% CI)	Higher birth weight ≥3,912 g Mean (95% CI)	<i>p</i> value
	127				0.52 ²
Progesterone, ng/dl [‡]	3	117.79 (66.74, 207.91)	107.62 (79.06, 146.50)	83.70 (44.02, 159.14)	0.70 ¹
	127				0.62 ²
	3				
Follicular phase					
Estradiol, ng/dl [‡]	179	4.48 (3.51, 5.72)	4.33 (3.89, 4.81)	4.94 (3.59, 6.79)	0.76 ¹
	141				0.59 ²
	3				
Non-SHBG-bound estradiol, ng/dl [‡]	179	2.45 (1.90, 3.16)	2.17 (1.88, 2.51)	0.30 (1.66, 3.20)	0.64 ¹
	141				0.22 ²
	3				
Estrone, ng/dl [‡]	179	3.86 (3.28, 4.54)	3.45 (3.14, 3.78)	3.80 (3.09, 4.67)	0.31 ¹
	141				0.28 ²
	3				
Estrone sulfate, ng/dl [‡]	180	89.97 (70.58, 114.69)	80.71 (70.02, 93.05)	74.91 (54.78, 102.42)	0.59 ¹
	141				0.37 ²
	3				
Progesterone, ng/dl [‡]	175	31.26 (21.37, 45.72)	29.99 (23.98, 37.49)	29.41 (17.81, 48.56)	0.97 ¹
	141				0.66 ²
	3				
(b)					
Combined luteal and follicular phase					
Androstenedione, ng/dl [‡]	346	138.30 (124.05, 154.18)	128.23 (120.88, 136.02)	126.49 (111.39, 143.64)	0.40 ¹
	205				0.16 ²
	3				
Testosterone, ng/dl [‡]	343	31.97 (27.88, 36.66)	29.58 (27.81, 31.47)	29.15 (24.81, 34.25)	0.38 ¹

	<i>n</i> samples <i>n</i> individuals (max samples per individual)	Lower birth weight ≤2,892 g Mean (95% CI)	Average birth weight 2,920–3,884 g Mean (95% CI)	Higher birth weight ≥3,912 g Mean (95% CI)	<i>p</i> value
	205				0.37 ²
DHEAS, lg/dl [‡]	3				
	347	124.21 (106.40, 145.01)	106.03 (97.89, 114.85)	108.14 (90.38, 129.39)	0.17 ¹
	205				0.31 ²
SHBG, nmol/dl [‡]	3				
	348	61.65 (52.50, 72.38)	63.12 (58.13, 68.53)	67.56 (56.13, 81.32)	0.74 ¹
	205				0.38 ²
Luteal phase	3				
Estradiol, ng/dl [‡]	162	10.04 (7.51, 13.43)	10.26 (8.76, 12.01)	11.03 (7.91, 15.37)	0.90 ¹
	127				0.55 ²
Non-SHBG-bound estradiol, ng/dl [‡]	3				
	162	5.04 (3.83, 6.61)	5.14 (4.43, 5.96)	5.68 (4.15, 7.76)	0.82
	127				0.48 ²
Estrone, ng/dl [‡]	3				
	162	5.50 (4.37, 6.94)	5.22 (4.62, 5.91)	5.68 (4.37, 7.38)	0.79 ¹
	127				0.92 ²
Estrone sulfate, ng/dl [‡]	3				
	165	130.86 (96.15, 178.11)	137.04 (116.37, 161.40)	157.51 (112.98, 219.60)	0.68 ¹
	127				0.52 ²
Progesterone, ng/dl [‡]	3				
	160	117.79 (66.74, 207.91)	107.62 (79.06, 146.50)	83.70 (44.02, 159.14)	0.70 ¹
	127				0.62 ²
Follicular phase	3				
Estradiol, ng/dl [‡]	179	4.14 (3.18, 5.39)	4.02 (3.47, 4.65)	4.65 (3.32, 6.52)	0.69 ¹
	141				0.61 ²

	<i>n</i> samples <i>n</i> individuals (max samples per individual)	Lower birth weight ≤2,892 g Mean (95% CI)	Average birth weight 2,920–3,884 g Mean (95% CI)	Higher birth weight ≥3,912 g Mean (95% CI)	<i>p</i> value
Non-SHBG-bound estradiol, ng/dl [‡]	3				
	179	2.45 (1.90, 3.16)	2.17 (1.88, 2.51)	2.30 (1.66, 3.20)	0.65 ¹
	141				0.23 ²
Estrone, ng/dl [‡]	3				
	179	3.86 (3.28, 4.54)	3.45 (3.14, 3.78)	3.80 (3.09, 4.67)	0.31 ¹
	141				0.32 ²
Estrone sulfate, ng/dl [‡]	3				
	180	89.97 (70.58, 114.69)	80.71 (70.02, 93.05)	74.91 (54.78, 102.42)	0.64 ¹
	141				0.41 ²
Progesterone, ng/dl [‡]	3				
	175	31.26 (21.37, 45.72)	29.99 (23.98, 37.49)	29.41 (17.81, 48.56)	0.98 ¹
	141				0.86 ²
	3				

SD standard deviation, *CI* confidence interval, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate

^a Items in the same row marked with the same letter differ at $p \leq 0.05$

¹ *p* value for categorical birth weight;

² *p* value for continuous birth weight

[†] Geometric means and 95% CI adjusted for visit number, treatment group, and age; estrogens and progesterone adjusted for menstrual cycle day

[‡] Geometric means and 95% CI adjusted for visit number, treatment group, age, years since menarche; estrogens and progesterone adjusted for menstrual cycle day