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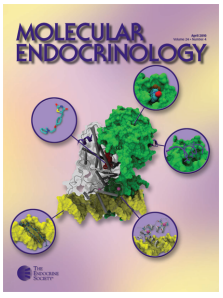

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Effects of Birth Weight on Anti-Müllerian Hormone Serum Concentrations in Infant Girls

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Context: We previously demonstrated that low birth weight (BW) infant girls show increased serum anti-Müllerian hormone (AMH) concentrations and poststimulated estradiol levels compared to normal-BW infants, suggesting an altered follicular development. However, the impact of high BW on reproductive function is less known.

Objective: To evaluate the effect of BW on AMH, we determined the concentrations of this hormone in low-BW, normal-BW, and high-BW female infants during the first 3 months of life.

Design: Twenty-seven low-BW, 29 normal-BW, and 28 high-BW infant girls were studied. We measured serum gonadotropins, steroid hormones, AMH, glucose, insulin, free fatty acids, IGF-I, and adiponectin in a fasting blood sample. In addition, in a subgroup of normal-BW (n = 23) and high-BW infants (n = 10), a GnRH analog leuprolide acetate test was performed.

Results: Serum concentrations of AMH were higher in low-BW and high-BW infants compared to normal-BW infants ($P = 0.028$ and 0.022, respectively). In addition, in high-BW infants, adiponectin concentrations were lower ($P = 0.018$), and poststimulated FSH and estradiol levels were higher compared to normal-BW infants ($P = 0.024$ and 0.047, respectively).

Conclusions: Serum AMH and poststimulated estradiol concentrations are increased in low-BW and high-BW female infants, suggesting that these girls may show evidence of an altered follicular development. However, the increased poststimulated FSH levels and low adiponectin concentrations observed in high-BW infants suggest that ovarian function is perturbed through a different mechanism from that in low-BW infants. (***J Clin Endocrinol Metab*** **95: 903–910, 2010)**

Epidemiological studies in humans have shown that low birth weight (BW) is associated with an increased risk for several disorders arising later in life, such as cardiovascular disease, type 2 diabetes, obesity, and hypertension (1–6). These observations have led to the concept that adult disease originates *in utero* as a result of changes in development during suboptimal intrauterine conditions, often associated with impaired fetal growth (7). The process by which early insults at critical stages of development lead to permanent changes in tissue structure and function is known as intrauterine programming.

Animal studies and human epidemiological data show that this programming phenomenon occurs across the normal range of BW, with the worst prognoses at the extremes (8). In this regard, recent findings in different populations demonstrate that high BW and low BW are associated with diabetes (9, 10). This results in a U-shaped curve with higher diabetes rates in both tails of the distribution. Although it is now recognized that

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Abbreviations: AMH, Anti-Müllerian hormone; BMI, body mass index; BW, birth weight; 17-OHP, 17-hydroxyprogesterone; PCOS, polycystic ovary syndrome; SDS, SD score(s).

high-BW infants are at risk of developing type 2 diabetes and cardiovascular disease (11), the impact of high BW on reproductive function is less clear.

It has been proposed that impaired fetal growth is associated with reproductive disorders in both sexes, which could arise early during fetal development. In females, low BW has been associated with impaired ovarian development (12–14), oligoovulation and anovulation (15), and polycystic ovary syndrome (PCOS) (16–19). In a recent pilot study, we observed an increase in anti-Müllerian hormone (AMH) serum concentrations during early infancy in low-BW girls, suggesting that these girls may show evidence of an altered follicular development from a very early age (20).

In the present study we extended these observations to a greater number of low-BW and normal-BW infant girls, and included a new group of high-BW female infants. The aim of the present study was to evaluate AMH serum concentrations during the first 3 months of life in low-BW, normal-BW, and high-BW female infants born to apparently healthy women to study the effect of BW on AMH serum concentrations. In addition, we assessed several metabolic parameters, and in a subgroup of infants we studied the pituitary-ovarian axis by the GnRH analog leuprolide acetate test.

Subjects and Methods

Subjects

This study is part of a larger ongoing project in which endocrine and metabolic variables are studied in healthy children born in Santiago, Chile, corresponding to a demographic area serving a lower-middle class population. Although, many women were interviewed, we included only those who agreed to participate in this study. Women with spontaneous singleton pregnancies were recruited during the third trimester of pregnancy or after delivery from two university hospitals in Santiago. Information regarding maternal medical history, smoking, parity, nutritional status, gestational diabetes, and hypertension was obtained from hospital records and at least two medical interviews. Only infants born to apparently healthy women without any of the above-mentioned factors were included in the study. We excluded from this study women with other endocrine disorders such as PCOS, thyroid and adrenal disorders, and hyperprolactinemia. Gestational age was based on menstrual history and/or ultrasound and was confirmed by physical examination (21).

In the present study we included 27 low-BW, 29 normal-BW, and 28 high-BW infant girls. From these girls, 10 low-BW and 15 normal-BW were included in our previous study (20). All girls were born at term. Infants were defined as low-BW infants if their BW was below the 10th percentile, normal-BW infants if their BW was above the 25th and below the 75th percentile, and high-BW infants if their BW was above the 90th percentile, using Chilean BW reference standards (6, 22). Preterm infants and those showing evidence of malformations or genetic disorders were excluded from the study.

Study protocol

All infants were examined twice, once during the first 3 d of life and again at 2–3 months of age. During the first physical exam, gestational age and anthropometric measurements including weight, length, and head circumference were recorded. SD scores (SDS) were calculated using local normative data (22). Weight was measured with a manual scale with a 10-g graduation (Seca, Hamburg, Germany), and supine length was measured using an infantometer. A tape measure was used to measure head circumference.

At the age of 2 to 3 months, all infants were admitted with their mothers to our Clinical Research Center at approximately 0830 h. We performed a complete physical examination on each baby, including anthropometric measurements, following the same scheme described at birth. Anthropometric parameters at 2–3 months of age were analyzed with the Growth Analyser program (2004 version), and height and weight SDS were calculated using the National Center for Health Statistics (NCHS) growth standards, which have been shown to be applicable to the Chilean population (23). During this visit, breastfeeding was continued *ad libitum*, and the schedule was recorded for each infant.

In all infants, a fasting blood sample (4 h after the last feeding) was obtained by venipuncture from an antecubital vein. In those girls whose mothers agreed, we performed a GnRH analog leuprolide acetate test [normal-BW infants (n = 23) and high-BW infants (n = 10)], as previously reported in low-BW infants (20). LH and FSH were measured at baseline and 3 and 24 h after leuprolide administration. Serum testosterone, 17-hydroxyprogesterone (17-OHP) and estradiol were determined at baseline and 24 h after the leuprolide challenge. Serum AMH, glucose, insulin, free fatty acids, IGF-I, and adiponectin were measured at baseline.

The protocol was approved by the Institutional Review Boards of the San Juan de Dios Hospital, San Borja Arriarán Hospital, and the University of Chile. All parents signed informed consents before their daughters entered the study.

Assays

Serum LH, FSH, and estradiol were determined by electrochemiluminescence (Roche, Basel, Switzerland). Assay sensitivities were 0.1 IU/liter, 0.1 IU/liter, and 5.0 pg/ml, respectively. Intra- and interassay coefficients of variation were 1.8 and 5.2% for LH; 1.8 and 5.3% for FSH; and 5.7 and 6.2% for estradiol, respectively.

Serum testosterone (Diagnostic Systems Laboratories, Webster, TX), androstenedione (Diagnostic Systems Laboratories), and 17-OHP (Diagnostic Products Corp., Los Angeles, CA) were assayed by RIA. Assay sensitivities were 0.1, 0.1, and 0.1 ng/ml, respectively. Intra- and interassay coefficients of variation were 9.6 and 8.6% for testosterone; 5.6 and 9.8% for androstenedione; and 3.5 and 8.5% for 17-OHP, respectively.

Serum AMH was assayed by enzyme immunoassay (Immunotech-Beckman Coulter, Marseille, France). Assay sensitivity was 2.1 pmol/liter and intra- and interassay coefficients of variation were 5.3 and 8.7%, respectively.

Serum adiponectin (Linco-Research Inc., St Charles, MO) and insulin (Diagnostic Systems Laboratories) were assayed by

RIA with a sensitivity of 1.0 ng/ml and 3.0 μIU/ml, respectively. Intra- and interassay coefficients of variation were 1.8 and 9.0% for adiponectin and 5 and 8% for insulin, respectively. Serum IGF-I was determined by immunoradiometric assay with a first acid extraction step (Diagnostic Systems Laboratories). The sensitivity of this assay was 4.5 ng/ml. Intra- and interassay coefficients of variation were 3.0 and 1.5%, respectively.

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche). The intraassay coefficient of variation was less than 2.0%. Serum free fatty acid was determined by colorimetric assay (Biovision Research Products, Mountain View, CA). The intra- and interassay coefficients of variation were 4 and 6%, respectively.

Statistical analysis

Data are expressed as median and range. Normal distribution was assessed by the Kolmogorov-Smirnov test. Categorical data were analyzed using χ^2 or Fisher's exact test. Differences between normal-BW and low-BW or high-BW were assessed by the Student's *t* test when data were normally distributed, or by the Mann-Whitney test for data not normally distributed. Maximal values after leuprolide were defined as the peak value for gonadotropins at 3 h, and for steroids at 24 h after stimulation. The association between continuous variables was assessed through Spearman correlation analysis. Statistical analysis was performed with STATA 7.0 package (StataCorp, College Station, TX). A *P* value of less than 0.05 was considered to be statistically significant.

Results

Clinical characteristics

Table 1 shows the clinical characteristics of the three groups of pregnant women. There were no significant differences between groups in maternal characteristics such as age and height. However, pregnant women with high-BW infants showed a higher body mass index (BMI) at the beginning and at the end of pregnancy (third trimester), compared with women with normal-BW infants. Weight gain during pregnancy was not significantly higher in this group of women compared with women with normal-BW infants. Pregnant women with low-BW infants showed no significant differences in BMI at the beginning and at the end of pregnancy compared with women with normal-BW infants. Weight gain during pregnancy in this group of women was lower compared with women with normal-BW infants. On the other hand, 70.4% of the women with low-BW infants and 67.9% of the women with high-BW infants were primiparous, compared with 48.3% of the mothers of normal-BW infants ($P = 0.110$ and 0.182, respectively). There was a correlation between the mothers' BMI at the end of pregnancy and the BW of their newborns ($r = 0.406$; $P < 0.0001$).

Table 2 shows the clinical characteristics for normal-BW, low-BW, and high-BW infants at birth and at 2–3 months of age. As expected, head circumference, weight, and length in low-BW infants at birth were significantly lower than in normal-BW infants. The clinical characteristics of both groups of infants remained significantly different at 2–3 months of age, except for head circumference. In contrast, head circumference, weight, and length at birth and at 2–3 months of age in high-BW infants were significantly higher than in normal-BW infants.

Hormone levels

Table 3 shows the endocrine and metabolic parameters in the three groups of infants. Basal levels of gonadotropins and sex steroids were not significantly different between groups.

However, in high-BW infants, adiponectin concentrations were significantly lower ($P = 0.018$), and free fatty acid concentrations tended to be higher compared with normal-BW infants, but this difference did not achieve statistical significance ($P = 0.087$).

Serum concentrations of AMH are shown in Fig. 1. AMH concentrations were significantly higher in low-BW and high-BW infants compared with normal-BW infants [normal-BW, 11.3 (3.0–38.7) pmol/liter; low-BW, 18.1 (3.0–48.0) pmol/liter; and high-BW, 18.3 (3.0–53.5) pmol/liter ($P = 0.028$ and 0.022, respectively)] (Fig. 1).

Table 4 shows gonadotropin and sex steroid hormone levels in a subgroup of normal-BW, low-BW (previously published in Ref. 20), and high-BW female infants before

TABLE 1. Clinical characteristics of the mothers

	Normal BW	Low BW	*P* value	High BW	*P* value
n	29	27		28	
Age (yr)	26.0 (17.0 to 36.0)	25.0 (15.0 to 35.0)	0.148	26.0 (17.0 to 35.0)	0.990
Height (m)	1.6 (1.5 to 1.7)	1.6 (1.5 to 1.7)	0.652	1.6 (1.5 to 1.7)	0.365
Initial weight (kg)[a]	62.0 (46.0 to 91.0)	62.0 (47.0 to 85.0)	0.671	70.0 (54.0 to 100.0)	0.006
Initial BMI (kg/m^2)	24.7 (19.6 to 37.4)	25.6 (19.1 to 34.0)	0.733	27.4 (21.6 to 36.5)	0.021
Weight at term of pregnancy (kg)	77.0 (58.0 to 105.0)	74.0 (55.0 to 100.0)	0.833	86.0 (72.0 to 124.0)	0.006
BMI at term of pregnancy (kg/m^2)	30.8 (24.6 to 43.1)	30.1 (22.3 to 41.2)	0.474	33.8 (28.9 to 44.5)	0.019
Weight gain during pregnancy (kg)	15.0 (7.5 to 32.0)	12.0 (−1.0 to 20.0)	0.043	16.0 (1.0 to 28.0)	0.492

Values are expressed as median (range). Differences between normal- BW and low-BW or high-BW were assessed by the Student's *t* test when data were normally distributed or Mann-Whitney test for data not normally distributed.

[a] The initial weight of the mothers corresponds to the weight at the beginning of pregnancy.

TABLE 2. Clinical characteristics of normal-BW, low-BW, and high-BW infants at birth and at 2–3 months of age

	Normal BW	Low BW	*P* value	High BW	*P* value
n	29	27		28	
At birth					
Gestational age (wk)	39.0 (37.0 to 41.0)	39.0 (37.0 to 41.0)	0.117	39.5 (38.0 to 41.0)	0.104
BW (g)	3525 (2900 to 3920)	2600 (2170 to 2900)	<0.001	4335 (4070 to 5050)	<0.001
Weight SDS	0.3 (−1.1 to 1.2)	−1.9 (−3.3 to −1.4)	<0.001	2.9 (1.8 to 4.7)	<0.001
Length (cm)	50.0 (45.5 to 53.0)	47.0 (43.0 to 49.5)	<0.001	52.0 (50.0 to 55.0)	<0.001
Length SDS	0.2 (−1.1 to 1.4)	−1.0 (−3.2 to 0.1)	<0.001	1.4 (0.1 to 2.7)	<0.001
Head circumference (cm)	35.0 (32.0 to 38.0)	33.0 (30.0 to 34.0)	<0.001	36.0 (34.0 to 38.0)	0.001
At study					
Age (d)	75.0 (62.0 to 92.0)	80.0 (71.0 to 94.0)	0.128	78.0 (60.0 to 94.0)	0.380
Weight (g)	5840 (4100 to 7140)	4980 (4090 to 6200)	<0.001	6400 (5390 to 8160)	0.005
Weight SDS	1.0 (−1.3 to 3.2)	−0.5 (−1.7 to 1.2)	<0.001	1.7 (0.3 to 4.0)	0.010
Length (cm)	58.5 (55.5 to 62.0)	56.0 (53.0 to 59.5)	<0.001	60.5 (54.0 to 66.0)	0.002
Length SDS	0.2 (−0.9 to 1.6)	−0.9 (−2.2 to 0.1)	<0.001	0.9 (−1.4 to 2.9)	0.002
Head circumference (cm)	39.0 (34.0 to 42.0)	39.0 (36.5 to 41.0)	0.092	40.0 (36.5 to 42.5)	0.006

Values are presented as median (range). Differences between normal-BW and low-BW or high-BW were assessed by the Student's *t* test when data were normally distributed or Mann-Whitney test for data not normally distributed.

and after leuprolide administration. Basal concentrations of gonadotropins and sex steroids were similar between groups. After leuprolide administration, no significant differences were observed in LH, 17-OHP, androstenedione, or testosterone concentrations. However, low-BW and high-BW showed higher poststimulated estradiol levels compared with normal-BW female infants ($P = 0.048$ and 0.047, respectively). In addition, poststimulated FSH levels were higher in high-BW compared with normal-BW female infants ($P = 0.024$).

Spearman regression analysis showed that AMH exhibited a strong negative correlation with basal and poststimulated FSH in normal-BW ($r = -0.416$, $P = 0.034$; and $r = -0.572$, $P = 0.008$, respectively), low-BW ($r = -0.823$, $P < 0.001$; and $r = -0.845$, $P = 0.001$, respectively), and high-BW females ($r = -0.496$, $P = 0.019$; and $r = -0.810$, $P = 0.015$, respectively).

Discussion

In this study, we evaluated AMH serum concentrations and metabolic parameters in normal-BW, low-BW, and high-BW infant girls. We observed that low-BW and high-BW female infants exhibited higher basal AMH serum concentrations compared with normal-BW infants. In females, AMH is produced by the granulosa cells and reflects the size of the growing follicle pool (24). Serum AMH levels seem to correlate with the development of preantral and small antral follicles from puberty until the end of reproductive life (25), indicating that these girls appear to show evidence of an altered follicular development during early infancy. This is a novel observation that indicates that high-BW and low-BW may affect reproductive function, resulting in a U-shaped curve with possible ovarian dysfunction at both tails of the BW distribution curve.

TABLE 3. Basal gonadotropin and sex steroid concentrations, and metabolic parameters in normal-BW, low-BW, and high-BW infants at 2–3 months of age

	Normal BW	Low BW	*P* value	High BW	*P* value
n	29	27		28	
LH (IU/liter)	0.6 (0.1 to 3.5)	0.3 (0.1 to 1.3)	0.308	0.3 (0.1 to 0.9)	0.980
FSH (IU/liter)	5.6 (1.2 to 19.9)	5.9 (1.1 to 18.4)	0.867	7.0 (2.5 to 25.9)	0.348
17-OHP (ng/ml)	8.7 (3.7 to 13.6)	10.1 (1.0 to 16.8)	0.233	8.9 (4.8 to 14.6)	0.805
Androstenedione (ng/ml)	0.6 (0.1 to 2.9)	0.7 (0.1 to 2.0)	0.628	0.5 (0.2 to 1.4)	0.506
Testosterone (ng/ml)	0.3 (0.1 to 0.6)	0.2 (0.1 to 0.4)	0.086	0.2 (0.1 to 0.6)	0.096
Estradiol (pg/ml)	13.3 (5.0 to 32.1)	10.5 (5.0 to 21.8)	0.191	11.2 (5.0 to 20.2)	0.383
Glucose (mg/dl)	82.0 (55.0 to 111.0)	92.0 (82.0 to 97.0)	0.138	90.0 (73.0 to 104.0)	0.204
Insulin (μIU/ml)	9.9 (5.0 to 36.3)	9.0 (5.0 to 11.3)	0.513	9.8 (5.0 to 15.1)	0.965
Adiponectin (μg/ml)	36.5 (13.9 to 55.3)	37.0 (19.5 to 59.3)	0.857	30.0 (5.1 to 69.9)	0.018
Free fatty acids (mmol/liter)	0.3 (0.1 to 1.1)	0.4 (0.1 to 1.1)	0.571	0.5 (0.3 to 0.9)	0.087
IGF-I (ng/ml)	50.7 (8.3 to 118.4)	41.1 (8.9 to 87.7)	0.391	44.5 (22.6 to 74.6)	0.474

Values are median and range. Differences between normal-BW and low-BW or high-BW were assessed by the Student's *t* test when data were normally distributed or Mann-Whitney test for data not normally distributed.

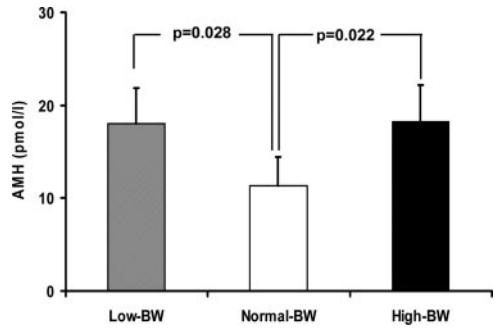

FIG. 1. AMH serum concentrations in normal-BW, low-BW, and high-BW infant girls at 2–3 months of age. Data are expressed as median ± SEM.

In a recent study, we found that serum AMH concentrations were increased in prepubertal daughters of women with PCOS, indicating that these girls appear to show evidence of an altered follicular development during infancy and childhood (26). In that study, we selected only normal-BW infants born to PCOS and control mothers to avoid the possible effect of abnormal fetal size on gonadal function because a relationship between reduced fetal size and PCOS has been suggested (17, 19).

We proposed that the elevated AMH concentrations in female infants of PCOS mothers and in low-BW infants reflect an excess number of growing follicles that may be present during intrauterine life, and may be a common reproductive phenotype and a possible link between intrauterine growth retardation and PCOS. Therefore, in high-BW infants, a link between large size at birth and subsequent development of PCOS is also possible. In agreement with this notion, de Zegher *et al.* (27) recently proposed that at least two developmental pathways seem to lead to PCOS. One of them, called the "postnatal-overweight" pathway, starts with relatively large size at birth and continues with the development of obesity during childhood and adolescence leading to the PCOS phenotype with polycystic ovaries. The other pathway, the so-called "prenatal-underweight" pathway, begins with fetal growth restraint, continues in infancy with rapid catch-up weight leading to increased adiposity, and finally to an adult PCOS phenotype without polycystic ovaries. According to the findings of the present study and the data from our previous study, we speculate that intrauterine programming may affect the reproductive function in low-BW and high-BW infant girls, albeit through possibly different mechanisms.

We observed higher poststimulated serum estradiol levels in high-BW infants, similar to those previously reported by us in low-BW infant girls. However, low-BW girls showed an increased estradiol response to leuprolide without increased FSH secretion, which suggests a gonadotropin-independent phenomenon. Thus, the underlying mechanism may be related to the presence of an increased follicular mass. Experimental studies have revealed significantly more oocytes in fetuses from nutritionally restricted ewes than in fetuses from adequately fed ewes (28). Based on this observation, Borwick *et al.* (28) proposed that the normal processes of oogonial degradation that occur at this time and cause a reduction in oocyte number may be delayed in undernourished fetuses. A similar mechanism may occur in low-BW infant girls.

TABLE 4. Basal and peak hormonal responses to leuprolide administration in normal-BW, low-BW, and high-BW infants at 2–3 months of age

	Normal BW	Low BW[a]	*P* value	High BW	*P* value
n	23	10		10	
LH (IU/liter)					
Basal	0.6 (0.1 to 3.5)	0.1 (0.1 to 0.3)	0.066	0.1 (0.1 to 0.1)	0.098
Peak	4.6 (1.5 to 12.9)	5.3 (1.9 to 14.3)	0.405	6.9 (2.7 to 12.0)	0.061
FSH (IU/liter)					
Basal	5.7 (1.2 to 19.9)	3.3 (1.1 to 11.5)	0.476	6.0 (3.2 to 9.6)	0.177
Peak	39.1 (15.7 to 91.0)	35.0 (10.5 to 58.1)	0.692	59.8 (26.9 to 96.8)	0.024
17-OHP (ng/ml)					
Basal	8.5 (3.7 to 12.1)	8.0 (1.0 to 15.8)	0.778	8.5 (4.8 to 14.6)	0.597
Peak	13.1 (5.7 to 25.7)	7.7 (4.7 to 14.0)	0.056	11.9 (4.5 to 21.6)	0.716
Androstenedione (ng/ml)					
Basal	0.6 (0.1 to 2.9)	0.7 (0.1 to 1.9)	0.676	0.5 (0.2 to 1.4)	0.734
Peak	0.7 (0.1 to 1.6)	0.8 (0.1 to 2.0)	0.329	0.7 (0.2 to 1.5)	0.818
Testosterone (ng/ml)					
Basal	0.3 (0.1 to 1.0)	0.1 (0.1 to 0.3)	0.135	0.3 (0.1 to 0.6)	0.910
Peak	0.2 (0.1 to 0.5)	0.2 (0.1 to 0.3)	0.526	0.3 (0.1 to 0.6)	0.856
Estradiol (pg/ml)					
Basal	13.2 (5.0 to 32.1)	7.4 (5.0 to 20.2)	0.122	12.2 (5.0 to 32.1)	1.000
Peak	30.7 (5.0 to 104.0)	41.3 (5.0 to 154.2)	0.048	45.5 (23.0 to 99.0)	0.047

Values are expressed as median (range). Differences between normal-BW and high-BW infants were assessed by Mann-Whitney. Maximal values after leuprolide were defined as the peak value for gonadotropins at 3 h, and for steroids at 24 h after stimulation.

[a] Data previously published in Ref. 20.

High-BW girls also showed an increase in the estradiol response to leuprolide, but in these girls we observed an increase in FSH concentrations, suggesting that the underlying mechanism that promotes estradiol secretion was different from that observed in low-BW infant girls. In a previous study (unpublished data), we established that LH levels were increased in response to leuprolide administration in high-BW male infants. Therefore, it is possible that the fetal neuroendocrine axis is perturbed in high-BW male and female infants, whereas this is not observed in low-BW infants.

The programming effect observed at the neuroendocrine and gonadal levels in high-BW infants could be related to endocrine-metabolic factors arising from the mother, the placenta, or the fetus. In this regard, we observed that pregnant women who delivered high-BW newborns showed a higher BMI at the beginning and at the end of pregnancy, compared with women who delivered normal-BW infants. Therefore, we documented a clear relationship between the BMI of the mother and of her newborn, which is in agreement with previous studies (29, 30). It is thought that obesity reduces insulin sensitivity and increases the availability of glucose for maternal-fetal transport (31), promoting intrauterine growth (32). Moreover, it has been demonstrated that obese women exhibit higher glucose levels during pregnancy than normal-weight women. Even if these glucose levels do not reach the range for gestational diabetes, the impact on the fetal pancreas is similar to that of gestational diabetes (33). In addition, a recent study suggests that high BMI and increased caloric intake alter the maternal circulation of metabolic hormones, which up-regulates placental nutrient transport and results in increased nutrient delivery to the fetus (34).

In large-for-gestational-age infants, leptin concentrations are increased, reflecting the size of the adipose tissue mass (35, 36). Because leptin may stimulate FSH release from the pituitary (37), it is possible that increased leptin levels in our high-BW infant girls may have promoted FSH release from the pituitary in response to GnRH. However, we cannot verify this hypothesis because we did not measure serum leptin concentrations in the present study.

We believe that FSH is probably not related to the increased serum AMH concentrations observed in these girls because basal FSH concentrations were not increased, and a negative correlation between FSH and AMH levels was observed in these girls, which is in agreement with several studies in adult women (38, 39). Interestingly, the three groups of infant girls showed a negative correlation between FSH and AMH independently of body weight, suggesting that this relationship is established early in life as previously described (20).

In the present study, high-BW infant girls showed significantly lower concentrations of adiponectin compared with normal-BW infant girls, reflecting decreased insulin sensitivity because circulating adiponectin concentrations are correlated with insulin sensitivity independent of BMI (40, 41). This is a novel finding, which suggests that adiponectin concentrations could serve as an early marker for metabolic derangement in these girls. Moreover, high-BW infant girls showed a tendency for higher free fatty acid levels. In addition, a recent study shows that fetuses of obese mothers were more insulin resistant than fetuses of lean mothers, which is in agreement with our observations (42). In contrast, in small-for-gestational-age infants compared with adequate-for-gestational-age infants, no differences in adiponectin levels have been described (43), which is in agreement with the present study.

Interestingly, in prepubertal daughters of PCOS women, we observed a similar constellation of findings (44) characterized by low adiponectin and increased AMH concentrations. How are these early metabolic and reproductive markers related? In high-BW infants, adiponectin levels are decreased, suggesting that the fetal tissues of these girls are probably exposed to high insulin levels. Considering that insulin has a known gonadotropic effect on ovarian tissue, we speculate that high AMH levels and low adiponectin levels are a reflection of high insulin levels during intrauterine life. In a previous study, we observed a positive correlation between insulin and AMH concentrations in peripubertal daughters of women with PCOS (45). This observation suggests a relationship between insulin and AMH levels, which is in agreement with a recent study performed in PCOS and non-PCOS women (46). Moreover, preliminary data from our group suggest that metformin administration to PCOS patients throughout pregnancy prevents the increase in AMH levels observed in their daughters (47). Therefore, it is possible that changes in insulin levels may affect AMH expression, or that improvements in metabolic control may lead to a reduction in ovarian follicular mass and to lower AMH levels.

Population-based studies have observed that increases in maternal BMI and decreases in maternal smoking may lead to an increase in the proportion of large-for-gestational-age infants (48). The prevalence of obesity among adolescents and young women and of high-BW infants may increase further in the future. Therefore, the identification of metabolic and reproductive markers may be very important for attempting to consider possible early interventions in these girls.

In summary, in low-BW and high-BW female infants, basal AMH serum concentrations are increased, suggesting that these girls may show evidence of an altered ovar-

ian follicular development. This is a novel observation that indicates that both ends of the BW distribution curve may affect reproductive function in females. Prospective studies are needed to establish the clinical significance of elevated AMH levels in large-for-gestational-age female infants and their possible relationship with subsequent reproductive disorders.

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