Early Metformin Therapy (Age 8–12 Years) in Girls with Precocious Pubarche to Reduce Hirsutism, Androgen Excess, and Oligomenorrhea in Adolescence

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Context: Girls with a combined history of low(-normal) birth weight (LBW) and precocious pubarche (PP) are at high risk to develop polycystic ovary syndrome (PCOS).

Objective: The objective of the study was to compare the capacity of early *vs.* late metformin treatment to prevent adolescent PCOS.

Design: This was a randomized, open-label study over 7 yr.

Setting: The study was conducted at a university hospital.

Patients: Thirty-eight LBW-PP girls were followed up from the mean age 8 until age 15 yr.

Intervention: Early metformin (study yr 1–4; age 8–12 yr) *vs.* late metformin (yr 6; age 13–14 yr).

Main Outcome Measures: Measures included height; weight; hirsutism score; menstrual cycle; endocrine-metabolic screening (fasting; follicular phase); C-reactive protein; body composition (absorptiometry); abdominal fat partitioning (magnetic resonance imaging); ovarian morphology (ultrasound); PCOS (National Institutes of Health and Androgen Excess Society definitions) after yr 7 (all girls thus untreated for at least 1 yr).

Results: None of the girls dropped out of the study. At age 15 yr, early-metformin girls were taller (4 cm), were in a less proinflammatory state, and had less central fat due to reductions in visceral and hepatic fat. Hirsutism, androgen excess, oligomenorrhea, and PCOS were between 2- and 8-fold more prevalent in late- than early-treated girls. Abdominal adiposity was the first variable to diverge (at age 8–10 yr) between girls without *vs.* with PCOS at age 15 yr.

Conclusions: In LBW-PP girls, early metformin therapy was found to prevent or delay the development of hirsutism, androgen excess, oligomenorrhea, and PCOS more effectively than late metformin. The time window of late childhood and early puberty may be more critical for the development, and thus for the prevention, of adolescent PCOS than the first years beyond menarche. **(*J Clin Endocrinol Metab* 96: E1262–E1267, 2011)**

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Abbreviations: AES, Androgen Excess Society; AMH, anti-Müllerian hormone; BMI, body mass index; CRP, C-reactive protein; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; HOMA-IR, homeostasis model assessment insulin resistance index; LBW, low birth weight; MRI, magnetic resonance imaging; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome; PP, precocious pubarche.

Evidence is converging to indicate that a lipid excess in adipose tissue is a major origin of androgen excess or polycystic ovary syndrome (PCOS) in adolescent girls and young women (1). This lipid excess may originate from combining a normal lipid-storage capacity with a chronically positive energy imbalance (as in simple obesity), from combining a low lipid-storage capacity with a normal energy intake (as in genetic lipodystrophies) or from combining a low-normal storage capacity with a high-normal energy intake [as in girls combining a low-normal birth weight with a high-normal body mass index (BMI)] (1). The latter subgroup is expanding swiftly and may already be the largest on a global scale, not so much because birth weights are decreasing but because BMIs are increasing, including in populations with a low capacity of sc lipid storage.

Precocious pubarche (PP; appearance of pubic hair before age 8 yr) is a classic referral point in the sequence from a low birth weight (LBW) to an early menarche and then onward to a PCOS phenotype and to an adult height below midparental level (2–5). It is in a cohort of such LBW-PP girls that we initiated a 7-yr study exploring the potential of metformin to prevent or delay the development of PCOS. In the first years of this study, we observed that early metformin therapy was accompanied by reductions of visceral and hepatic fat, by a less advanced menarche, and by a taller stature (6–9). Here we focus on the last years of this study, in particular on the emergence of PCOS features.

Study Population and Methods

Subjects and ethics

The study population consisted of 38 LBW-PP girls, distributed in two subgroups of 19 girls, whose baseline characteristics were comparable (Table 1) (6). In the total population, birth weight (mean ± SEM) was 2.4 ± 0.1 kg after 38.6 ± 0.4 wk gestation, age at diagnosis of PP 6.8 ± 0.2 yr, age at study start 7.9 ± 0.1 yr, bone age 9.0 ± 0.1 yr, height 129.4 ± 1.2 cm, weight 31.0 ± 0.9 kg, BMI 18.4 ± 0.3 kg/m^2, dehydroepiandrosterone sulfate (DHEAS) at PP diagnosis 102 ± 6 μg/dl, and post-ACTH 17-hydroxy-progesterone 274 ± 16 ng/dl. As described (6–9), the inclusion criteria were: 1) PP due to exaggerated adrenarche, as judged by high serum DHEAS and/or androstenedione levels; 2) weight below 2.9 kg at term birth (38–41 wk) or below −1 SD for gestational age at preterm birth (33–37 wk); 3) BMI less than 22 kg/m^2, which corresponds to the +2 SD cutoff in girls aged approximately 8 yr; and 4) prepuberty (Tanner stage B1). None of the girls had a family or personal history of diabetes or presented evidence for thyroid dysfunction, glucose intolerance, or adrenal hyperplasia; none was receiving a medication known to affect gonadal function or carbohydrate metabolism.

The study was registered as ISRCTN84749320 and was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu. Informed consent was obtained from parents and assent from girls.

Study design

The study design over 7 yr is summarized in Fig. 1. Girls were randomly assigned (10) to remain untreated for 4 yr or to receive early metformin for 4 yr (425 mg/d at dinnertime for 2 yr and then 850 mg/d for 2 yr) (6, 7). In the fifth study year, all girls were followed up without intervention (8). The early metformin girls also remained untreated in the sixth and seventh study years. In contrast, the originally untreated girls (all of whom were postmenarcheal by the end of the fifth study year) (8) received late metformin (850 mg/d) in the sixth study year and were again followed up without intervention in the seventh study year. At the end of study yr 7, all girls were thus untreated for at least 1 yr.

Assessments

Clinical examination, including height measurement with a Harpenden stadiometer, was performed every 6 months by the same clinician (L.I.). Age at menarche was derived by 6-monthly history.

Assessment of fasting insulin, IGF-I, SHBG, DHEAS, androstenedione, testosterone, lipid profile, and white blood cell count and assessment of body composition were each performed every 6 months for 2 yr and yearly thereafter. Serum C-reactive protein (CRP) and anti-Müllerian hormone (AMH) were assessed after yr 7.

Body composition was assessed by dual-energy x-ray absorptiometry with a Lunar Prodigy coupled to Lunar software (Lunar Corp., Madison, WI) (11).

From yr 5 of the study onward, sc and visceral fat areas were in the abdominal region assessed by magnetic resonance imaging (MRI) using a multiple-slice MRI 1.5 Tesla scan (Signa LX Echo Speed Plus Excite; General Electric, Milwaukee, WI) (8). From yr 6 onward, MRI was also used to assess the intrahepatic lipid content by comparing the relative intensity of the liver to that of sc fat and spleen, assuming that the latter is fat free (8). All the MRI scans were performed by the same operator (blinded to the treatment allocation), and all images were analyzed by the same radiologist (also blinded to the allocation).

The presence of polycystic ovarian morphology was assessed by abdominal ultrasound performed with a digital Sonoline G40 scanner (Siemens, Erlangen, Germany) and a 5-MHz multifrequence probe. Ultrasound studies were performed by a single observer (blinded to treatment allocation). Ovarian volume was calculated using the formula for a modified prolate ellipsoid. The ovarian morphology was considered to be polycystic when at least one ovary contained 12 or more follicles with a diameter between 2 and 9 mm and/or when mean ovarian volume was 10.0 ml or greater (12).

The presence of PCOS was judged by National Institutes of Health (NIH) criteria, requiring the presence of clinical/biochemical androgen excess and either oligomenorrhea (cycles >45 d) or amenorrhea (no menses for >3 months), besides exclusion of disorders known to potentially cause the same phenotype, such as hyperprolactinemia and 21-hydroxylase deficiency (13). The presence of PCOS was also judged by Androgen Excess Society (AES) criteria, requiring the presence of clinical/biochemical androgen excess and either oligomenorrhea/amenorrhea or a polycystic ovarian morphology (14).

TABLE 1. Outcomes in LBW girls with PP, who were studied over a time span of 7 yr

	Early metformin (0–4 yr)				Late metformin (5–6 yr)			
Birth weight (g)	2386 ± 107				2471 ± 116			
Birth weight Z-score	−1.8 ± 0.1				−1.7 ± 0.1			
Age at PP (yr)	5.4 ± 0.3				6.1 ± 0.3			
Age at menarche (yr)	12.5 ± 0.2				11.4 ± 0.1[a]			
	0 yr[b]	**7 yr**	**Δ 5–6 yr**	**Δ 6–7 yr**	**0 yr[b]**	**7 yr**	**Δ 5–6 yr**	**Δ 6–7 yr**
Distance to target height (cm)[c]	33.0 ± 1.9	−2.2 ± 1.2	1.7 ± 0.4	0.8 ± 0.2	33.6 ± 1.3	1.6 ± 1.4[d]	0.9 ± 0.2[e]	0.2 ± 0.1[e]
BMI Z-score	1.4 ± 0.4	0.9 ± 0.3	0.1 ± 0.1	0.2 ± 0.1	1.2 ± 0.3	1.7 ± 0.4[e]	−0.2 ± 0.2	0.4 ± 0.2
Ferriman-Gallwey score	—	6.9 ± 0.4	—	—	—	10.1 ± 0.8[a]	—	—
IGF-I (ng/ml)	197 ± 11	450 ± 23	−43 ± 35	−24 ± 28	215 ± 10	433 ± 21	−166 ± 23[f]	51 ± 19[e]
Fasting insulin (μU/ml)	8.6 ± 0.9	8.5 ± 1.1	−0.4 ± 0.9	−3.2 ± 0.8	8.2 ± 0.6	12.3 ± 1.5[e]	−3.2 ± 1.2[e]	0.8 ± 1.6[e]
HOMA-IR	1.9 ± 0.2	1.9 ± 0.3	−0.1 ± 0.2	−0.8 ± 0.2	1.8 ± 0.1	2.7 ± 0.3[e]	−0.8 ± 0.3[e]	0.1 ± 0.4[e]
SHBG (nmol/liter)	53 ± 5	36 ± 3	1 ± 2	2 ± 3	57 ± 4	29 ± 3	3 ± 3	−4 ± 1[e]
DHEAS (μg/dl)	104 ± 10	233 ± 21	35 ± 8	11.3 ± 8.9	95 ± 9	276 ± 14[e]	30 ± 8	6.2 ± 16.7
Androstenedione (ng/dl)	98 ± 7	302 ± 19	27 ± 14	9.1 ± 10.9	90 ± 5	333 ± 17	−15 ± 19[e]	22.7 ± 16.4
Testosterone (ng/dl)	32 ± 3	41 ± 3	−5 ± 5	−4 ± 4	28 ± 3	47 ± 5	−25 ± 6[e]	6 ± 5
LDL-cholesterol (mg/dl)	107 ± 7	94 ± 5	−3 ± 3	7 ± 3	102 ± 6	100 ± 5	−7 ± 5	12 ± 5
HDL-cholesterol (mg/dl)	60 ± 3	51 ± 2	0 ± 3	−3 ± 2	61 ± 3	47 ± 2	3 ± 5	−5 ± 5
Triglycerides (mg/dl)	74 ± 10	60 ± 4	2 ± 3	−7 ± 5	63 ± 7	79 ± 9[e]	−5 ± 8	−1 ± 6
White blood cell count ($10^3/\mu l$)	7.9 ± 0.4	7.1 ± 0.4	0.1 ± 0.3	−0.3 ± 0.1	7.6 ± 0.3	8.3 ± 0.4[d,f]	−0.1 ± 0.2	0.5 ± 0.3[e]
Neutrophil count ($10^3/\mu l$)	4.2 ± 0.3	3.7 ± 0.3	0.3 ± 0.2	−0.3 ± 0.1	3.6 ± 0.2	4.6 ± 0.3[d,f]	−0.2 ± 0.2[e]	0.5 ± 0.2[f]
CRP (mg/liter)	—	0.4 ± 0.1	—	—	—	1.6 ± 0.5[d]	—	—
AMH (ng/ml)	—	3.9 ± 0.5	—	—	—	4.3 ± 0.5	—	—
BMD (g/cm^2)	0.75 ± 0.02	1.17 ± 0.03	0.05 ± 0.02	0.01 ± 0.02	0.74 ± 0.02	1.16 ± 0.02	0.06 ± 0.02	0.02 ± 0.01
Lean mass (kg)	19.7 ± 0.7	36 ± 0.9	0.5 ± 0.3	0.6 ± 0.2	19.6 ± 0.5	34.5 ± 0.9	1.2 ± 0.5	−0.2 ± 0.5
Fat mass (kg)	10.8 ± 1.0	19.6 ± 1.5	1.7 ± 0.5	0.7 ± 0.6	10.3 ± 0.9	22.1 ± 1.8	−0.9 ± 0.9[e]	1.1 ± 0.7
Abdominal fat (kg)	3.0 ± 0.4	5.8 ± 0.4	0.4 ± 0.2	0.5 ± 0.2	2.8 ± 0.3	6.4 ± 0.5	−0.6 ± 0.3[f]	0.4 ± 0.3
Abd fat (% abd soft tissue mass)	19.7 ± 2.2	17.3 ± 1.2	−0.3 ± 0.3	0.8 ± 0.5	19.3 ± 1.7	24.3 ± 1.0[a,f]	−1.9 ± 0.7[e]	0.2 ± 0.7
Abd sc fat (cm^2)	—	156 ± 18	3 ± 6	18 ± 10	—	139 ± 16	−4 ± 8	7 ± 7
Abd visceral fat (cm^2)	—	32 ± 2	4 ± 2	−1.3 ± 0.2	—	39 ± 3	−9 ± 3[g]	−1.3 ± 0.4
Visceral to sc fat	—	0.25 ± 0.02	0.05 ± 0.02	−0.05 ± 0.03	—	0.33 ± 0.0[d]	−0.05 ± 0.02[f]	−0.01 ± 0.02
Intrahepatic lipid content (%)	—	11.5 ± 1.3	2.9 ± 1.5	0.1 ± 1.4	—	16.6 ± 1.5[d]	−2.0 ± 2.5	1.5 ± 1.9

At the age of 8 yr, LBW-PP girls were randomized into two subgroups: early-metformin girls (n = 19) received metformin for 4 yr and then remained untreated for 3 yr; late-metformin girls (n = 19) remained untreated for 5 yr and then received metformin for 1 yr and remained thereafter untreated for 1 yr. Focus here is on study yr 6 and 7. Values are mean ± SEM. *Dashes* indicate that measurements were not performed at the time given. BMD, Bone mineral density; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Abd, abdominal.

[a] $P \leq 0.001$ between subgroups after 7 yr of study.

[b] No significant differences between randomized subgroups at start.

[c] Target height was calculated as midparental height, adjusted for gender (paternal height −13 cm) and secular trend (+3 cm).

[d] $P < 0.05$ between subgroups after 7 yr of study.

[e] $P < 0.05$ between subgroups for 0–7 yr, 5–6 yr, or 6–7 yr change (Δ).

[f] $P \leq 0.01$ between subgroups for 0–7 yr, 5–6 yr, or 6–7 yr change (Δ).

[g] $P \leq 0.001$ between subgroups for 0–7 yr, 5–6 yr, or 6–7 yr change (Δ).

Hormone assays and statistics

Serum immunoreactive insulin, IGF-I, SHBG, DHEAS, androstenedione, and testosterone were assayed by immunochemiluminiscence (IMMULITE 2000; Diagnostic Products, Los Angeles, CA) (5); the intra- and interassay coefficients of variation (CV) were between 4 and 8%. CRP was assessed by a highly sensitive method (Architect c8000; Abbott, Wiesbaden, Germany) with intra- and interassay CV below 2% and a detection limit of 0.1 mg/liter. Serum AMH was assessed using a second-generation enzyme immunoassay (AMH-EIA; Immunotech, Marseille, France; reference A16507). Recombinant human AMH was used as a calibration standard to build a standard curve ranging from 0 to 21 ng/ml. The intra- and interassay CV were 12 and 14%, respectively. Samples from randomized subgroups were assayed concomitantly.

Statistical analyses were performed with SPSS 12.0 (SPSS, Chicago, IL). Student's *t* tests and χ^2 tests were used to compare outcomes between subgroups and general linear model for repeated measures to compare changes between subgroups. For uniformity, results are expressed as mean ± SEM. The level of significance was set at $P < 0.05$.

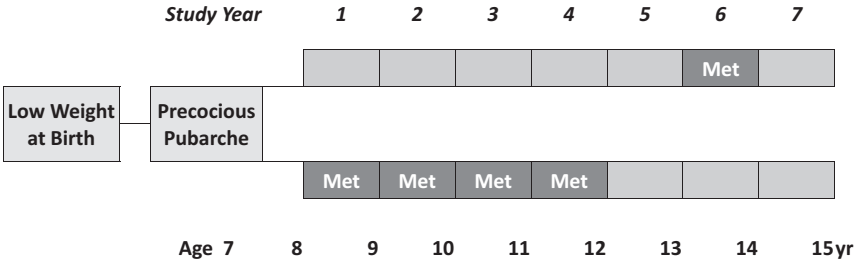

FIG. 1. Study design. Girls with a combined history of low birth weight and precocious pubarche (n = 38) were randomized at a mean age of 8 yr for either early treatment (age 8–12 yr; n = 19) or late treatment (age 13–14 yr; n = 19) with metformin (Met). All girls remained untreated in other study years.

TABLE 2. Features of PCOS in girls with a combined history of LBW and PP, who were treated with metformin either early (age 8–12 yr) or late (age 13–14 yr)

	Early metformin (n = 19)		Late metformin (n = 19)	
	n	%	n	%
Androgen excess				
Ferriman Gallwey score >8	2	11[a]	12	63
Serum testosterone above +2 SD (>48 ng/dl)[b]	6	32[c]	12	63
Total (clinical and/or biochemical)	6	32[c]	13	68
Menstrual irregularity				
Amenorrhea (no menses for >3 months)	0	0	0	0
Oligomenorrhea (cycles >45 d)	1[d]	5[e]	7[d]	37
Total (amenorrhea or oligomenorrhea)	1[d]	5[e]	7[d]	37
Polycystic ovaries (by ultrasound)				
Mean ovarian volume ≥10.0 ml	3	16	3	16
≥12 cysts (2–9 mm) in one or both ovaries	0	0	1	5
Total (by volume and/or cyst number)	3	16	4	21
PCOS				
NIH definition	1[d]	5[e]	7[d]	37
AES definition	1[d]	5[e]	8[d]	42

[a] $P \leq 0.001$ for early *vs.* late metformin.

[b] Limit of +2 SD derived from healthy girls in early follicular phase; n = 18; age 16.9 ± 0.3 yr; BMI 21.2 ± 0.5 kg/m^2.

[c] $P \leq 0.05$ for early *vs.* late metformin.

[d] All girls with oligomenorrhea and/or PCOS were more than 2 yr beyond menarche.

[e] $P \leq 0.01$ for early *vs.* late metformin.

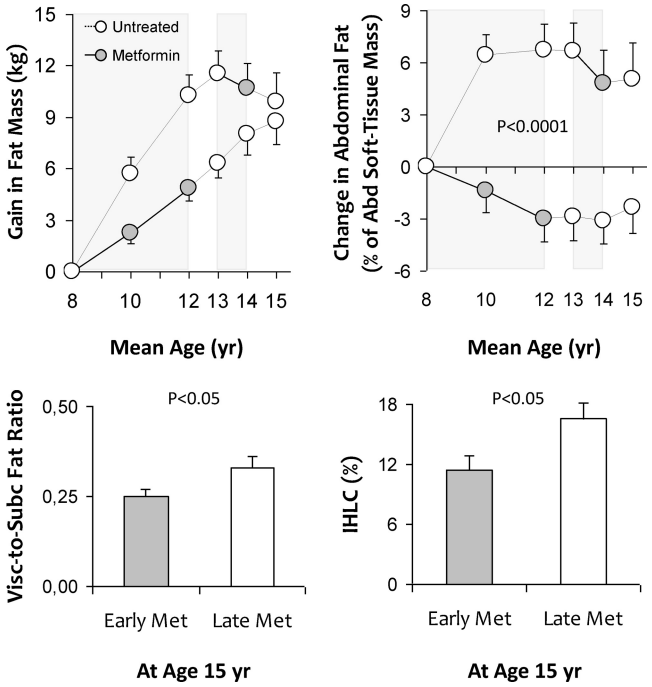

FIG. 2. Longitudinal observations in girls with a combined history of low birth weight and precocious pubarche (n = 38), here subgrouped by early treatment (age 8–12 yr; n = 19) *vs.* late treatment (age 13–14 yr; n = 19) with metformin. After 7 yr of study, the gain in total fat mass was similar in early- and late-treated girls (*upper-left panel*). Early metformin treatment was accompanied by a reduction of abdominal adiposity, which appeared to persist up to age 15 yr (*upper-right panel*) and to be due to a (relatively) lower amount of visceral and hepatic fat (*lower panels*). Abd, Abdominal; visc, visceral; subc, subcutaneous; Met, metformin; IHLC, intrahepatic lipid content. Data are shown as mean and SEM.

Results

Tables 1 and 2 show that, after 7 yr of study, the early-metformin girls were taller (about 4 cm), were in a less proinflammatory state (as judged by CRP and neutrophil count), had a less central fat distribution (due to reductions of visceral and hepatic fat; Fig. 2), and had a lower prevalence of PCOS (due to lower prevalences of hirsutism, hyperandrogenemia, and oligomenorrhea). Over the 7 study years, early-metformin girls had lower increments of BMI Z-score, fasting insulin, homeostasis model assessment insulin resistance index (HOMA-IR), DHEAS, and triglycerides (Table 1). Late metformin therapy was accompanied by normalizing changes, most of which did not persist on stopping metformin. The timing of metformin treatment did not detectably influence either the circulating AMH levels (Table 1) or the ovarian morphology (Table 2).

At age 15 yr, close correlations were observed among central-adiposity markers, CRP, HOMA-IR, and SHBG in the total study population (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

By definition, LBW-PP girls with PCOS differ from those without PCOS at age 15 yr (Supplemental Table 2). Figure 3 illustrates two early divergences between girls with *vs.* without subsequent PCOS. Abdominal adiposity was the first variable to diverge (age 8–10 yr). Circulating androstenedione was the first androgen to diverge, 2 yr after abdominal adiposity (age 10–12 yr) but still 3–5 yr before adolescent PCOS.

Discussion

Seven years after its initiation, the present study offered a first opportunity to test metformin's efficacy to prevent the development of adolescent hirsutism, androgen excess, menstrual irregularity, and PCOS. At age 15 yr, hirsutism, hyperandrogenemia, oligomenorrhea, and PCOS (by NIH and AES definitions) were found to be 2- to 8-fold more prevalent in LBW-PP girls who received a late and brief metformin treatment (age 13–14 yr) than in those

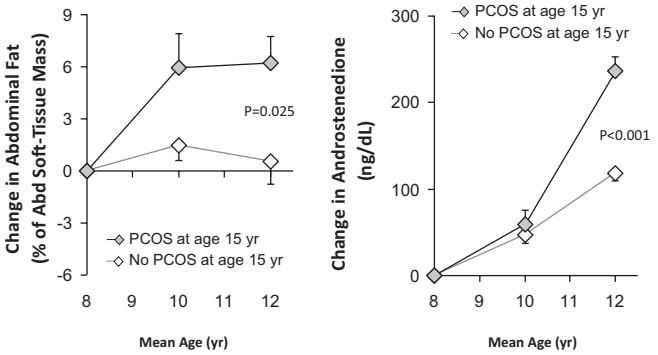

FIG. 3. Longitudinal observations in girls with a combined history of low birth weight and precocious pubarche (n = 38), who either were treated with metformin between age 8 and 12 yr (n = 19) or were not (n = 19). Irrespective of such treatment, the girls are subgrouped here by the presence (n = 9) or the absence (n = 29) of PCOS at age 15 yr. Abdominal adiposity diverges between PCOS subgroups by age 10 yr, and circulating androstenedione diverges by age 12 yr. For results at 8 and 15 yr, see Supplemental Table 2. Data are shown as mean and SEM.

who received an early and longer treatment (age 8–12 yr). These observations suggest, in accord with experience in obese and nonobese girls, (10, 15, 16) that the window of late childhood and early puberty is more critical for the development of PCOS features than the window shortly beyond menarche.

The mechanisms whereby early metformin therapy appears to reduce the prevalence of PCOS features in LBW-PP adolescents is still a matter of conjecture. However, two lines within the present evidence indicate that an early reduction of intraabdominal fat plays a pivotal role. Firstly, metformin therapy was associated with a marked and apparently persisting reduction of abdominal adiposity (Fig. 2, *upper right panel*), and this reduction occurred in visceral and hepatic fat (Fig. 2, *lower panels*) and not in sc fat (Table 1). Second, abdominal adiposity was the sole among all the assessed variables to diverge before age 10 yr between girls with *vs.* without subsequent PCOS, irrespective of metformin treatment (Fig. 3, *left panel*).

In the present cohort, AMH levels were at age 15 yr comparable in early- *vs.* late-metformin girls and also similar in girls with *vs.* without PCOS. These findings align well with recent evidence indicating that circulating AMH is a poor predictor not only of polycystic ovary morphology or PCOS in adolescents, (17) but also of androgen excess among oligomenorrheic adolescents (18).

As expected, the prevalence of a polycystic ovarian morphology was relatively low in the present study population. Indeed, ovarian volume is known to be reduced in adolescent girls and young women with low birth weight (19, 20). Similarly, the prevalence of a polycystic ovarian morphology (which is partly defined by ovarian volume) is also reduced in hyperandrogenic adolescents and young women with low birth weight (21, 22). These reductions are less obvious, but still discernible (de Zegher, F., and R. Legro, unpublished reappraisal), in morbidly obese women who self-report their birth weight and gestational age several decades after birth (23).

Further follow-up of the present cohort should disclose whether early metformin intervention did indeed reduce the prevalence of PCOS features or whether it merely postponed their emergence. In the meantime, our data corroborate the notion that adipose tissue hyperexpansion plays a key role in the pathogenesis of PCOS (1, 24, 25), and they provide pioneering support for the hope that PCOS's development can be prevented or postponed by intervention in late childhood and early puberty. We speculate that prevention of obesity in childhood and puberty will also reduce the prevalence of obesity-linked PCOS in adolescence. Together early lifestyle measures in obese girls and early metformin therapy in nonobese girls with a low fat-storage capacity should be able to diminish the prevalence of PCOS in adolescence and adulthood.

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