16 YEAR-OLD OBESE FEMALE WITH OLIGOMENORRHEA

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ENDORAMA

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Disclosures

- No financial interests.

- Will discuss the off-label use of Metformin for polycystic ovary syndrome in adolescents.

Chief Complaint

- 16 and 1/12th year old female with excessive weight gain in the last several years presents with concerns regarding irregular menstrual cycles.

History of Present Illness

- Puberty history:
  - Pubic hair: 11 years old
  - Breast development: 11 years old
  - Menarche: 12 years old
    - Menses every 4-6 months, each period lasting 1-5 days

- Other symptoms:
  - Always "heavyset" but has had "excessive weight gain in the last several years."
  - Decreased activity level
  - Denies acne, excessive hair growth, hair loss
  - Denies polydipsia, polyuria

Past Medical History

Birth History:

- Full-term, C-section, uncomplicated pregnancy and delivery
- BW: 8-lb (70 %), BL: 21 in (93 %)

Past Medical History:

- Acanthosis Nigricans – dx at 13 yo
- Hyperlipidemia – dx at 13 yo

Surgeries: None

Medications: None

Diet:

- 2-3 cans regular soda/day + 3 cups juice/week

Family History:

- Father: 43 yo, 6'6'', 200 lb, BMI 23
- Mother: 45 yo, 5'7'', 230 lb, BMI 36
  - Menarche at 11 yo
- Mid-Parental Height: 177 cm (70 in)
- 3 half siblings: healthy
- Maternal Aunt - infertility

Social History:

- Entering 10th grade, on Honor Roll
- Activity:
  - Watches < 2 h TV/day

Review of Systems

- General: Normal appetite, +decreased activity level, +weight gain. No fatigue.
- HEENT: Denies headaches, vision or hearing problems.
- CV: Denies chest pain, palpitations.
- Chest: Denies galactorrhea.
- Pulmonary: Negative.
- Gastrointestinal: Denies abdominal discomfort, nausea, vomiting, diarrhea, and constipation.
- Genitourinary: Denies polyuria, polydipsia. +Irregular menstrual cycles.
- MSK: Denies bone pain, joint pain, lower extremity edema.
- Neurologic: Denies nervousness, jitteriness, sleep problems.
- Skin: Denies acne, dry skin, excessive hair growth, hair loss.

Physical Exam

- VS: T 37.2C, P69, BP 103/65, Ht 174.7 cm (~95%), Wt 101.9 kg (>97%), BMI 33.4 (>97%).

- General: Well-appearing, no distress, overweight. No deepened voice.

- HEENT: Amblyopia right eye – unable to fully abduct right eye. No thyromegaly.

- Chest/Axilla: Tanner IV axillary hair, Tanner V breast. No nipple discharge.

- CV: Regular rate and rhythm, no murmur appreciated.

- Pulmonary: Clear to auscultation bilaterally.

- Abdomen: Soft, normal bowel sounds, non-tender, non-distended.

- Neurologic: Alert and oriented. Normal muscle tone. Patellar reflexes 2+ bilaterally.

- Skin: Acanthosis nigricans on neck, chest, and back. No acne. Pale striae on arms and abdomen.

- Ferriman-Gallwey Score: 6/36 (*no specific mention of hair distribution*)

Problem List

- Obesity
- Irregular Menses
- Physical exam findings concerning for insulin resistance

Differential Diagnosis

- Polycystic Ovary Syndrome (PCOS)
- Non-classic congenital adrenal hyperplasia (CAH)
- Hyperprolactinemia
- Hypothyroidism
- Partial ovarian failure
- Pregnancy
- Idiopathic hyperandrogenism
  - Obesity
  - Hereditary effects

- Cushing's Syndrome
- Growth hormone excess
- Insulin resistance disorders
  - T2DM
  - Lipodystrophy
- Virilizing tumors
- Other disorders of adrenal steroid metabolism:
  - Glucocorticoid resistance
  - Cortisone reductase deficiency
  - DHEA sulfotransferase deficiency

Initial Laboratory Studies

- Sodium 133 mEq/L, Rest of chem nl

- Serum glucose (random): 72 mg/dL

- Non-fasting Insulin: 70 mIU/mL (normal fasting 8 +/- 3)

- Cholesterol Panel:
  - TC: 203 mg/dL
  - TG: 89 mg/dL,
  - HDL: 34 mg/dL
  - LDL: 151 mg/dL

- Thyroid Function Tests:
  - TSH 3.3 mIU/mL (normal 0.3-3.8)
  - FTI 9.5 (normal 6-10.5)
  - T4: 8 mcg/dL (normal 5-11.6)

- Cortisol (random): 6.4 mcg/dL

- Prolactin: 10 ng/mL

□ <u>OGTT to screen for Diabetes Mellitus:</u>

	0 min	30 min	60 min	90 min	120 min	180 min
Glucose (mg/dL)	84	165	102	124	114	96
Insulin (mcU/mL)	11					

	Normal Range	16 1/12 yo (12 PM)
LH		13 mIU/mL
FSH		5.2 mIU/mL
Total Testosterone	19-70 ng/dL	153
Free Testosterone	3-10 pg/mL	44
Testosterone Binding Globulin	12-63 nM	6
DHEA-S	73-366 mcg/dL	115
Androstenedione	40-240 ng/dL	304
Estradiol	30-400 pg/mL	52

Dexamethasone Suppression Test

Treated with 2 mg
dexamethasone for 7 days:

	Baseline	s/p Dexamethasone
Total Testosterone (range 19-70 ng/dL)	153	118
Free Testosterone (range 3-10 pg/mL)	44	40
TBG (range 12-62 nM)	6	8
Cortisol (mcg/dL)	6.4	0.5
DHEA-S (73-366 mcg/dL)	115	20

Pelvic Ultrasound

- Both ovaries are about 16 cc, each containing more than 10 follicles per section. The largest follicle is 7 mm on the right and 5 mm on the left side.

Problem List

- Obesity
- Physical findings of insulin resistance
- Irregular Menses
- Mild hirsutism
- Hyperandrogenemia – presumed ovarian source
- Hyperinsulinism
- Polycystic ovaries

What are the appropriate diagnostic criteria for polycystic ovary syndrome (PCOS) in adolescents?

15 diseases doctors often get wrong

Health.com

By **Amanda MacMillan**, Health.com
September 3, 2014 -- Updated 1435 GMT (2235 HKT)

GETTY IMAGES

Polycystic Ovary Syndrome (PCOS)

- Lifelong, clinically heterogeneous disorder that includes the following constellation of symptoms:
    - Irregular menses
    - Symptoms of hyperandrogenism
    - Polycystic ovaries
    - Insulin resistance
- Symptoms typically begin around the time of puberty
- Affects 4-8 % of women of reproductive age

Azziz et al. JCEM. 2004. 89:2745-2749.
Franks et al. Int J Androl. 2006. 29:278-285.

Diagnostic Criteria for PCOS in Adults

- **<u>Rotterdam Consensus Criteria (2003):</u>**
- 2/3 Required:
  1. Oligo- and/or anovulation
  2. Clinical and/or biochemical signs of hyperandrogenism
  3. Polycystic ovaries
- Exclusion of disorders that mimic PCOS

Rotterdam … Human Reproduction. 2004;19:41.

The Challenges of Diagnosing PCOS in Adolescents

- Several features of "hyperandrogenism" may be normal transitory findings in adolescence
  - Severe acne
  - Irregular menstrual cycles
- Unlike in adults, there is typically no clear hirsutism or symptoms of hair loss in adolescents.
- Prompt diagnosis is not always possible

Diagnostic Criteria for PCOS in Adolescents

- <u>Hyperandrogenism:</u> Preferably biochemical confirmation
  - Free testosterone > 2 SD above the mean

AND

- <u>Abnormal menstrual pattern</u>: Persists 2 years after menarche
  - Primary amenorrhea: no menarche by 15 yo
  - Secondary amenorrhea: > 90 days without menses
  - Oligomenorrhea (abnormal # of cycles/year - determined by year after menarche)
  - Anovulatory abnormal uterine bleeding

Back to Our Case…

- <u>Treatment:</u>
  - Provera 10 mg daily x 1 week
  - Decreased caloric intake/Exercise for weight loss

- <u>16 + 7/12 years old:</u>
  - Menstrual period x 10 days s/p Provera
  - Reccs: start OCP (Yasmin)

	16 + 3/12 yo (Baseline)	16 + 11/12 (OCP)
Total Testosterone (ng/dL)	153	65
Free Testosterone (pg/mL)	44	9
TBG (nM)	6	57

Follow-Up

- <u>16 + 11/12 years old:</u>
  - Reports monthly periods on Yasmin, but c/o headaches, breast tenderness, bloating, nausea, mood swings
  - Reccs: stop OCP, reassess androgens, start Metformin XL 500 mg, up-titrate to 1000 mg BID

What is the role of Metformin in the treatment of PCOS in adolescents?

Treatment for PCOS in Adolescents

- Oral Contraceptives
  - Estrogen-progesterone
  - Progestin
- Weight management strategies
- Anti-androgen:
  - Spironolactone
- Treatment of insulin resistance
  - Metformin

Variability in treatment of adolescents with PCOS among pediatric providers

Table 3
Comparison of Treatment Recommendations for PCOS across 3 Pediatric Specialties

	Pediatric Endocrinology (n = 60) n (%)	Adolescent Medicine (n = 61) n (%)	Pediatric and Adolescent Gynecology (n = 60) n (%)	P Value*
Lifestyle changes	51 (85)	38 (62)	24 (40)	<.0001
Hormonal contraceptives	50 (83)	58 (95)	58 (97)	.015
Metformin	54 (90)	15 (25)	23 (38)	<.0001
Dietician	34 (57)	28 (46)	18 (30)	.013
Anti-androgen	12 (20)	1 (2)	6 (10)	.001

* Comparison across specialties was analyzed by chi-square testing. Significance defined as $P < .01$ due to multiple comparisons.

Auble et al. Ped Adol Gynecol. 26 (2013):234-238

Variability in treatment of adolescents with PCOS among pediatric providers

Table 4

Factors Associated with Recommendation for Metformin and Hormonal Contraceptives

	Odds Ratio	95% CI
Metformin		
Specialty		
PGyn vs PEndo	0.10	0.04, 0.30
AMed vs PEndo	0.04	0.01, 0.12
Obesity (>95th percentile BMI)	4.20	1.79, 9.86
Hormonal contraceptives		
Specialty		
PGyn vs PEndo	5.80	1.20, 27.73
AMed vs PEndo	3.87	1.01, 14.83

CI, Confidence interval; AMed, Adolescent Medicine; BMI, Body mass index; PEndo, Pediatric Endocrinology; PGyn, Pediatric and Adolescent Gynecology

Auble et al. Ped Adol Gynecol. 26 (2013):234-238

Metformin for PCOS in adolescents

ARTICLE

Randomized Placebo-Controlled Trial of Metformin for Adolescents With Polycystic Ovary Syndrome

Tracey Bridger, MD, FRCPC; Suzanne MacDonald, MD, FRCPC;
Franziska Baltzer, MD, FRCPC; Celia Rodd, MD, FRCPC

Metformin for PCOS in adolescents

Table 1. Clinical Characteristics and Serum Hormone Concentrations in Adolescents With PCOS at Baseline

Characteristic	Metformin Group	Placebo Group
Age, mean ± SD, y	16.07 ± 0.97	16.08 ± 1.39
Body mass index, mean ± SD*	33.6 ± 5.6	30.81 ± 3.0
Ferriman and Gallwey score, mean ± SD	5.3 ± 5.0	7.2 ± 7.6
Total testosterone, mean ± SD, ng/dL (nmol/L)	174.3 ± 54.0 (6.03 ± 1.88)	167.3 ± 46.0 (5.80 ± 1.58)
Insulin AUC, mean ± SD, μU/mL · min (pmol/L · min)	15 246 ± 10 097 (109 374 ± 72 433)	15 460 ± 12 377 (110 905 ± 88 788)
Fasting glucose, mean ± SD, mg/dL (mmol/L)	77.9 ± 7.2 (4.33 ± 0.4)	80.6 ± 8.3 (4.48 ± 0.46)
HOMA, mean ± SD	5.75 ± 10.08	2.79 ± 1.45
QUICKI, mean ± SD	0.34 ± 0.07	0.36 ± 0.05
Total cholesterol, mean ± SD, mg/dL (mmol/L)	164.9 ± 27.5 (4.25 ± 0.71)	171.1 ± 48.9 (4.41 ± 1.26)
LDL cholesterol, mean ± SD, mg/dL (mmol/L)	88.5 ± 19.8 (2.28 ± 0.51)	93.5 ± 41.9 (2.41 ± 1.08)
HDL cholesterol, mean ± SD, mg/dL (mmol/L)	45.8 ± 18.6 (1.18 ± 0.48)	42.3 ± 10.9 (1.09 ± 0.28)
Triglycerides, mean ± SD, mg/dL (mmol/L)	133.9 ± 55.1 (1.53 ± 0.63)	168 ± 77.9 (1.92 ± 0.89)
Ethnicity, No.		
White, non-Hispanic	7	10
Black, non-Hispanic	2	0
Hispanic	1	0
Asian	1	1
Menses in 6 months before enrollment, No.	2	3
Girls with menses during 6 months before enrollment, No.	2	3

Abbreviations: AUC, area under the curve; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PCOS, polycystic ovarian syndrome; QUICKI, quantitative insulin sensitivity check index.
*Body mass index is calculated as weight in kilograms divided by the square of height in meters.

Bridger et al. Arch Pediatr Adolesc Med. 2006. 16:241-246.

Metformin for PCOS in adolescents

Table 2. Change From Baseline in Clinical Characteristics and Blood Tests After Administration of Metformin or Placebo for 12 Weeks

Characteristic	Mean Difference		95% Confidence Interval for the Mean Difference Between Groups
	Metformin Group	Placebo Group	
Body mass index*	−0.16	−0.19	−1.01 to 0.32
Ferriman and Gallwey score	0	0	NA
Total testosterone, ng/dL	−38.3	−0.86	−∞ to −0.29
Insulin AUC, µU/mL · min	−3662	2093	−17531 to 6024
Fasting glucose, mg/dL	0.31	0.36	−3.42 to 5.22
HOMA	−1.06	0.86	−9.26 to 5.42
QUICKI	0.00	−0.01	−0.03 to 0.05
Total cholesterol, mg/dL	−0.78	−8.15	−17.07 to 31.82
LDL cholesterol, mg/dL	−3.10	−7.76	−12.80 to 20.56
HDL cholesterol, mg/dL	6.98	−2.33	0.78 to 18.23
Triglycerides, mg/dL	−13.13	7.00	−70.00 to 29.75
Girls with restored menses, No.	10/11	4/11	1.12 to 5.58 (relative risk, 2.50)

Abbreviations: AUC, area under the curve; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; NA, not applicable; QUICKI, quantitative insulin sensitivity check index.
*Body mass index is calculated as weight in kilograms divided by the square of height in meters.

Bridger et al. Arch Pediatr Adolesc Med. 2006. 16:241-246.

Metformin for PCOS in adolescents

ORIGINAL ARTICLE

Endocrine Care

The Impact of Metformin, Oral Contraceptives, and Lifestyle Modification on Polycystic Ovary Syndrome in Obese Adolescent Women in Two Randomized, Placebo-Controlled Clinical Trials

Kathleen Hoeger, Kristen Davidson, Lynda Kochman, Tracy Cherry, Laurie Kopin, and David S. Guzick

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Metformin alone

TABLE 3. Baseline and 24-wk measures for subjects completing single treatment trial

	MET (n = 6)		PL (n = 10)		OC (n = 10)		LS (n = 8)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
BMI (kg/m²)	35.0 ± 8.2	35.7 ± 8.6	34.9 ± 6.7	35.5 ± 6.8	37.8 ± 5.3	36.4 ± 5.4[a]	36.0 ± 6.2	34.9 ± 7.0
Waist (cm)	100.5 ± 11.8	105.3 ± 13.9	104.7 ± 15.9	105.3 ± 18.6	108.8 ± 14.7	108.3 ± 16.1	110.9 ± 14.2	109.9 ± 17.3
Total T (ng/dl)	47.8 ± 15.1	49.7 ± 31.1	64.4 ± 31.4	71.6 ± 33.8	62.0 ± 24	34.5 ± 28.6[b]	60.7 ± 23.6	64.5 ± 30.2
SHBG (nmol/liter)	18.6 ± 8.9	21.1 ± 8.4	17.1 ± 7.5	19.1 ± 9.4	16.1 ± 10.3	93.2 ± 66.5[b]	14.4 ± 14.9	32.0 ± 21.7[a]
FAI	10.8 ± 5.6	10.9 ± 7.9	15.6 ± 8.9	16.8 ± 11.2	19.1 ± 13.5	2.4 ± 2.5[b]	23.2 ± 16.6	9.5 ± 5.3[a]
FG score	8.3 ± 3.1	8.2 ± 3.4	11.6 ± 4.5	11.6 ± 4.9	10.2 ± 3.5	8.6 ± 2.1	9.1 ± 1.5	8.2 ± 2.0
Total CH (mg/dl)	152 ± 22.9	145.3 ± 25	167 ± 25.5	157 ± 53.2	165 ± 22.5	188.6 ± 20.7[b]	158.5 ± 29	156.2 ± 31
HDL (mg/dl)	40.2 ± 14.9	43.5 ± 19	40.7 ± 5.1	43.6 ± 8.9	36.2 ± 3.7	47.6 ± 9.9[b,d]	40.9 ± 10.3	40.4 ± 7.6
LDL (mg/dl)	100.3 ± 19.2	92.0 ± 15.5	117.0 ± 22.0	114 ± 27.1	117.8 ± 20.5	128.6 ± 37.5[a,c]	107.6 ± 26.5	101.2 ± 32.3
TG (mg/dl)	94.8 ± 27.1	71.3 ± 21.1[a]	93.7 ± 30.6	87.1 ± 25.1	91.5 ± 41.2	96.1 ± 41.1	93.9 ± 31.7	109.6 ± 67.9
FI (iU/ml)	20.8 ± 10.9	19.8 ± 10.4	26.4 ± 17.9	29.1 ± 24.5	24.1 ± 7.6	20.7 ± 10.6	27.7 ± 16.4	22.0 ± 10.5
AUC glu	23,404 ± 5,329	19,373 ± 3,553	19,004 ± 2,625	18,721 ± 2,285	20,056 ± 2,228	19,567 ± 2,735	18,440 ± 3,178	17,843 ± 4,229
AUC ins	11,902 ± 3,755	12,661 ± 8,041	33,748 ± 26,512	32,538 ± 27,386	26,507 ± 10,961	18,580 ± 9,499[b]	32,119 ± 21,400	20,726 ± 16,153
FBS (mg/dl)	91.6 ± 7.9	84.9 ± 12.7[a]	87.6 ± 9.0	86.5 ± 5.4	89.7 ± 7.6	82.8 ± 9.8	81.4 ± 5.4	81.8 ± 9.1
SBP (mm Hg)	121.7 ± 13.8	122.7 ± 8.9	114.4 ± 11.7	117.5 ± 12.9	116.4 ± 18.6	124.1 ± 14.5	111 ± 9.7	119 ± 14.5
DBP (mm Hg)	74 ± 12.9	65 ± 8.6	65.3 ± 6.6	63.3 ± 4.7	67.4 ± 7.8	70.1 ± 8.3	70 ± 8.9	60.7 ± 9.4[a]
CRP (mg/liter)	3.6 ± 2.7	2.8 ± 2.0	4.28 ± 3.1	4.2 ± 2.8	6.8 ± 6.1	9.5 ± 7.4[a]	4.5 ± 3.8	3.8 ± 3.6
PAI-1	49.7 ± 37.9	45.4 ± 32.2	40.3 ± 26.1	48.0 ± 45.9	46.9 ± 31.9	29.5 ± 20.6[a]	72.1 ± 38.4	45.0 ± 25.6[a]

MET, Metformin; PL, placebo; LS, lifestyle; T, testosterone; FG, Ferriman-Gallwey; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; FI, fasting insulin; glu, glucose; ins, insulin.

[a] $P < 0.05$ compared to baseline.

[b] $P < 0.01$ compared to baseline.

[c] $P < 0.05$ compared to LS.

[d] $P < 0.05$ compared to LS, PL, and MET.

Hoeger et al. JCEM. 2008; 93(11): 4299-4306.

Metformin + LS + OC versus Placebo + LS + OC

TABLE 5. Baseline and 24-wk measures for subjects completing combination treatment trial

	PL (n = 16)		MET (n = 16)	
	Pre	Post	Pre	Post
BMI (kg/m^2)	35.1 ± 4.9	33.9 ± 4.2[b]	34.3 ± 4.6	32.4 ± 4.8[b]
Waist (cm)	111.1 ± 8.9	109.7 ± 8.4	110.1 ± 10.2	106.2 ± 11.7[a]
Total T (ng/dl)	83.3 ± 27.7	55.7 ± 32.5[a]	102.6 ± 22.1	44.9 ± 21.4[c,d]
SHBG (nmol/liter)	10.1 ± 12.5	68.1 ± 55.8[c]	9.5 ± 11.5	82.9 ± 52.4[c]
FAI	6.3 ± 5.2	1.1 ± 2.0[b]	8.7 ± 5.9	0.4 ± 0.6[c]
FG score	10.2 ± 4.6	7.0 ± 3.6[c]	8.4 ± 3.0	6.2 ± 1.9[c]
Total CH (mg/dl)	160.6 ± 43.3	182.0 ± 47.7[a]	160.4 ± 39.5	201.1 ± 42.9[b]
HDL (mg/dl)	37.2 ± 10.5	49.4 ± 13.1[c]	39.6 ± 10.6	57.9 ± 12.5[c,d]
LDL (mg/dl)	97.2 ± 34.4	104.4 ± 39.5	96.0 ± 33.8	115.4 ± 38.6[a]
TG (mg/dl)	132.4 ± 84.4	150.5 ± 112.8	110.9 ± 91.8	148.2 ± 64.3
FI (IU/ml)	52.9 ± 66.1	38.4 ± 37.4	36.6 ± 40.4	38.3 ± 39.5
AUC ins	34,234 ± 20,738	26,688 ± 9,761	31,325 ± 27,942	31,808 ± 37,371
AUC glu	18,104 ± 2,836	20,081 ± 9,761	18,973 ± 3,218	19,693 ± 3,222
FBS (mg/dl)	89.6 ± 17.5	82.2 ± 6.1	90.1 ± 15.4	81.6 ± 7.1
SBP (mm Hg)	118.8 ± 12.6	115.7 ± 13.1	118.6 ± 12.5	119.2 ± 13.3
DBP (mm Hg)	63.8 ± 10.1	62.1 ± 11.0	66.2 ± 10.4	63.1 ± 5.1
CRP (mg/liter)	4.2 ± 5.5	8.0 ± 19.3	4.1 ± 4.6	12.3 ± 21.5[a]
TG/HDL	3.8 ± 2.5	3.2 ± 2.6	3.4 ± 3.5	2.6 ± 1.6

PL, Placebo; MET, metformin; T, testosterone; FG, Ferriman-Gallwey; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; FI, fasting insulin; glu, glucose; ins, insulin.

[a] $P < 0.05$ compared to baseline.

[b] $P < 0.01$ compared to baseline.

[c] $P < 0.001$ compared to baseline.

[d] $P < 0.05$ compared to PL.

Hoeger et al. JCEM. 2008; 93(11): 4299-4306.

Summary

- PCOS is a common syndrome among women and we should be aware of the diagnostic criteria to make an appropriate diagnosis of PCOS in adolescent patients

- There may be benefit for the use of Metformin for the treatment of PCOS symptoms in adolescents, but further large-scale studies are needed.

Works Cited

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