

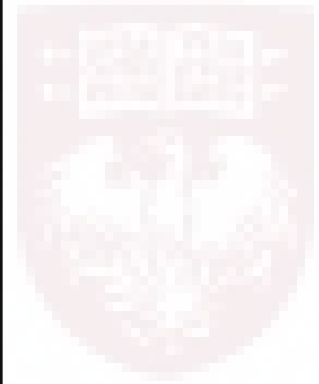
THE UNIVERSITY OF
CHICAGO
MEDICINE

8yo F with sexual precocity

Payal Patel, M.D.
Pediatric endocrinology fellow
November 21, 2013

Chief Complaint

- ▶ 8 3/12yo F with h/o sexual precocity presents for a 3rd opinion



THE UNIVERSITY OF
CHICAGO
MEDICINE



HPI

- ▶ First seen at 5 1/2 yrs for evaluation of pubic hair and body odor



THE UNIVERSITY OF
CHICAGO
MEDICINE



Review of Systems

- ▶ No headaches, visual disturbances, or weakness
- ▶ Mild acne. No other skin lesions
- ▶ No hair changes, temperature intolerance, weight change
- ▶ No noted breasts
- ▶ No height acceleration
- ▶ No vaginal discharge
- ▶ No known exposure to hormone containing products



Past Medical History

- ▶ Full-term, AGA for weight and length
- ▶ Uncomplicated pregnancy and delivery
- ▶ Normal development
- ▶ Allergic rhinitis
- ▶ Lactose intolerance
- ▶ PE tubes @ 18 mos of age
- ▶ Meds: none
- ▶ Allergies: NKDA



Social and Family History

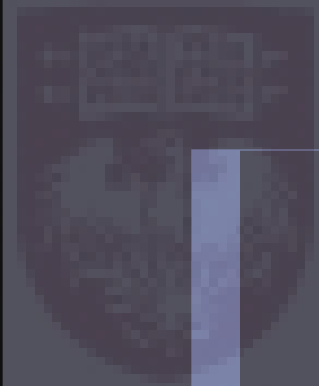
- ▶ Lives with parents and 2 healthy brothers.
- ▶ Father's ht: 5'10.5". Normal timing of puberty.
- ▶ Mother's ht: 5'7.5". Normal timing of puberty, menarche at 14 yrs.
- ▶ No family history of early puberty, childhood deaths, fertility problems, diabetes or other metabolic disorders



PE

- ▶ Vitals: within nL, Wt 70th%, Ht 60th%, BMI 20 (93rd%)
- ▶ General: well-nourished, NAD
- ▶ Neck: **No thyromegaly**
- ▶ CV/Resp/Chest: RRR, no murmur, CTAB, **Tanner I breasts, no axillary hair**
- ▶ GU: **nL external F genitalia, Tanner 2 pubic hair**
- ▶ Neuro: alert, no focal deficits
- ▶ Skin: warm, dry, nL pigmentation, no rash
- ▶ Psychiatric: nL mood, affect and behavior





THE UNIVERSITY OF
CHICAGO
MEDICINE

Differential Diagnosis?

DDx for Premature Pubarche

- ▶ Idiopathic premature pubarche
- ▶ Premature adrenarche
- ▶ Late-onset congenital adrenal hyperplasia
- ▶ Androgen-secreting tumor
- ▶ Exogenous hormones
- ▶ True precocious puberty



Evaluation for Premature Pubarche

- ▶ Idiopathic premature pubarche
- ▶ Premature adrenarche
- ▶ Late-onset congenital adrenal hyperplasia
- ▶ Androgen-secreting tumor
- ▶ Exogenous hormones
- ▶ True precocious puberty
- ▶ Bone age
- ▶ DHEAS
- ▶ 17-OH progesterone, consider ACTH stim
- ▶ AD, DHEAS, testosterone
- ▶ LH, FSH, E2, consideration of Lupron stim test
- ▶ TSH, FT4



Results of Evaluation

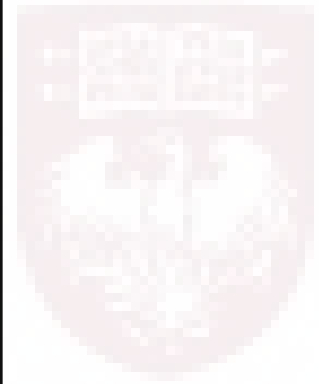
- ▶ Bone age: NL by report
- ▶ Adrenal U/S: NL
- ▶ DHEA 337 (< 377)
- ▶ DHEAS 164 (< 34)
- ▶ Androstendione 69 (6-115)
- ▶ Total testosterone 4 (< 8)
- ▶ Free testosterone 8.3 (4.5-12.5)
- ▶ TSH 2.20
- ▶ T4 8.3

ASSESSMENT?



Assessment/Plan

- ▶ Results consistent with premature adrenarche
- ▶ Observation advised



THE UNIVERSITY OF
CHICAGO
MEDICINE



HPI cont'd

- ▶ Seen for a 2nd endocrine opinion at 5 11/12 yrs
- ▶ Increased pubic hair, continued body odor, no noted breast development
- ▶ PE: NL vitals (BP 92/60), Wt (60th%), Ht (70th%)
- ▶ Prominent thyroid
- ▶ “Some breast tissue but no breast buds” → lipomastia?
- ▶ Tanner 1 axillary hair, Tanner 2 pubic hair
- ▶ NL neuro exam



Impression and Plan

- ▶ DDX: Premature adrenarche vs precocious puberty
- ▶ Plan: Labs, Bone age and possible Lupron stimulation test



THE UNIVERSITY OF
CHICAGO
MEDICINE



Evaluation at 6 1/12yrs

- ▶ Bone age repeated: read as 6 10/12yrs by radiology but 8 3/12yrs by endo
 - ▶ Predicted height = 60"
- ▶ Pelvic U/S: prepubertal configuration
- ▶ MRI: possible L-sided microadenoma, no additional abnormalities

Labs:

- ▶ ACTH 35
 - ▶ Cortisol 21.3
 - ▶ Prolactin 19.3 (<12)
 - ▶ TSH 2.07, FT4 1.2
 - ▶ Anti-TG/TPO Ab negative
 - ▶ LH 0.038 (0.02-0.3)
 - ▶ FSH 0.516 (1.0-4.2)
 - ▶ Estradiol <1
 - ▶ Total testosterone 16 (<10)
 - ▶ DHEA 575 (19-592)
-



Lupron Stim Test at 6 3/12yrs

	Time 0	60 min	120 min	180 min
FSH	0.424	5.1	8.0	9.8
LH	0.017	0.743	0.965	0.976
Estradiol	2.2			<1.0
Testosteron e	13			11

No 24-hr estradiol



Lupron Stimulation Test at 6 3/12yrs

	Time 0	60 min	120 min	180 min
FSH	0.424 (0.5-2.9)	5.1 (5.7-18)	8.0	9.8 (9.3-37)*
LH	0.017 (0.1-0.3)	0.743 (0.9-4.1)	0.965 (0.2-2.9)	0.976
Estradiol	2.2 (5-8)			<1.0
Testosterone	13 (<10)			11

Prepubertal normal values

*at 4-hrs

HPI cont'd

- ▶ Pubertal axis interpreted to be “activated”
- ▶ Plan for repeat bone age and Lupron suppression if bone age advanced
- ▶ Bone age at 6 4/12yrs = 8 4/12yrs
 - ▶ Predicted height = 61.5” (previously 60” at 8 3/12yrs)
- ▶ Question of breast tissue at this time by mother
- ▶ Supprelin implant placed at 6 5/12yrs





HPI cont'd

Follow-up at 6 9/12yrs

- ▶ Testosterone 12 (<10), DHEA 588 (19-592), BA 8 10/12yrs (61.2")
- ▶ Tx: Started Metformin 250mg QD

Follow-up at 7 3/12yrs

- ▶ Testosterone 13, DHEA 558, BA 9yrs (63")
- ▶ Tx: Increased Metformin to 250mg BID
- ▶ Plan: 17OHP, AD and possible cosyntropin stim test at next visit

Follow-up at 7 11/12yrs

- ▶ Testosterone 16, **DHEA 853**, 17OHP 82(< 91), AD 79 (<10-17)
 - ▶ LH 0.22, FSH 0.8, estradiol 1.3, BA 10 6/12yrs (60.7")
 - ▶ Assessment: Likely 3BHSD deficiency
 - ▶ Plan: Metformin 500mg BID, started Arimidex, replaced Supprelin
-



U of C: 3rd opinion at 8 3/12yrs

- ▶ Cont'd pubic hair growth, body odor, and possible breast development
- ▶ ROS as per HPI and otherwise unremarkable
- ▶ On Metformin, Arimidex, and Supprelin

Physical exam

- ▶ Wt 35.8 kg (92nd%), Ht 134.1 cm (80th%), BMI 20 (93rd%)
 - ▶ +Adiposity, no breast tissue
 - ▶ Tanner 3 pubic hair
-



Assessment

- ▶ Most likely premature adrenarche with bone age advancement
- ▶ Need to further assess for late-onset CAH
- ▶ Impossible to comment on current pubertal status, but no definitive evidence of puberty prior to Supprelin implant



Labs 09:11 a.m.

- ▶ ACTH 30
- ▶ Cortisol 14
- ▶ 17OHP 76 (< 90)
- ▶ 17OH preg 328 (< 72)
- ▶ DHEA 553 (19-592)
- ▶ DHEAS 211 (< 92)
- ▶ AD 79 (6-115)
- ▶ Total Testosterone 16 (<36)
- ▶ Free Testosterone 1.1 (0.2-5.0)



Cosyntropin Stimulation Test

	Time 0	30 min	60 min
ACTH	81.5		
17OHpreg	1280	1570	1560
17OHP	283	271	258
DHEA	9.7	11	11
AD	107		
Cortisol	28.5	34.9	37.8



Cosyntropin Stimulation Test

3BHSD deficiency

	Time 0	30 min	60 min
ACTH	81.5		
17OHpreg	1280 (335-4100)*	1570	1560 (1763-2391)
17OHP	283	271	258
DHEA	9.7	11	11
AD	107		
Cortisol	28.5	34.9	37.8

precursor:product ratios (>10)

DHEA:AD = 0.09

17-OHpreg:17-OHP = 4.5

17OHpreg:F ratios

Baseline = 44.9 (>1700)

Stimulated = 41.3 (>1930)

Summary

Impression: 8 3/12yo F with premature adrenarche

▶ No clear signs of puberty but now on Supprelin

Plan: Remove Supprelin after 1-yr (from placement)

▶ Discontinue Arimidex

▶ Continue Metformin



Clinical Questions

- ▶ What is the role of Metformin in the tx of premature pubarche?

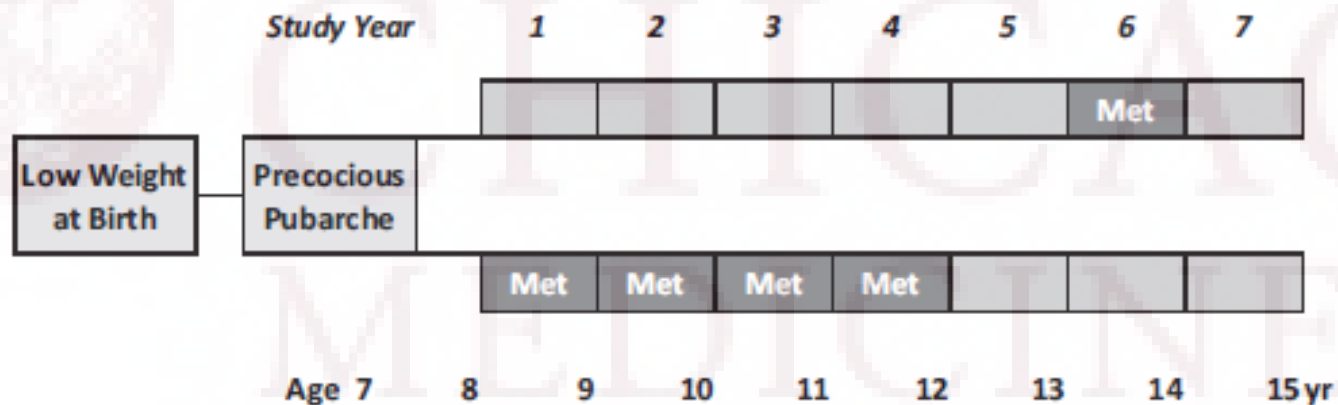


THE UNIVERSITY OF
CHICAGO
MEDICINE



Early vs. Late Metformin tx

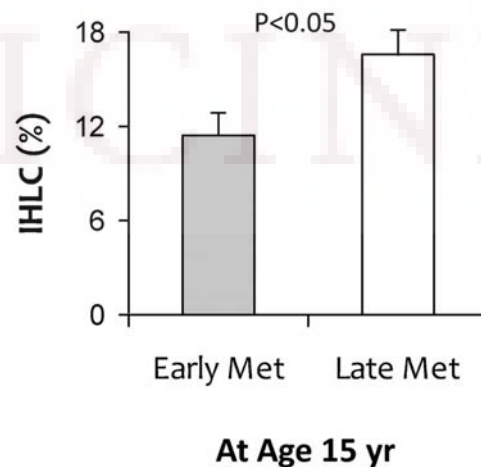
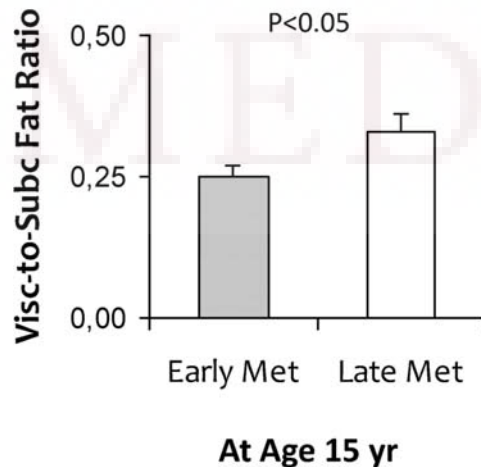
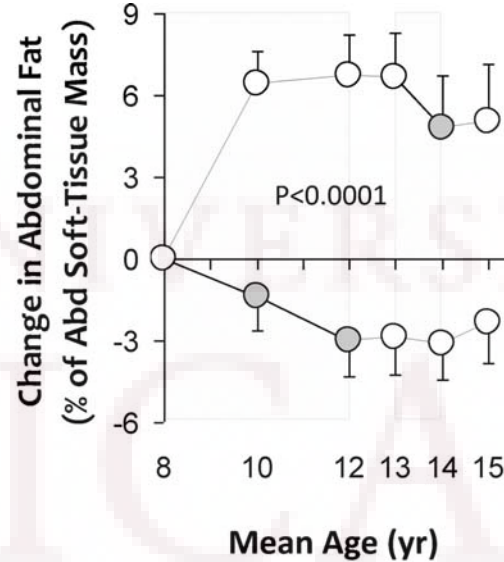
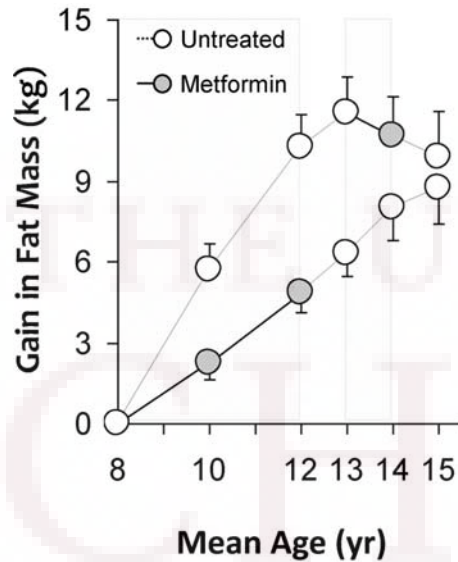
- ▶ 38 LBW females with precocious puberty
- ▶ Followed from age 8-15yrs
- ▶ Divided into 2 groups: early vs late Metformin tx



Outcomes in LBW-PP Females

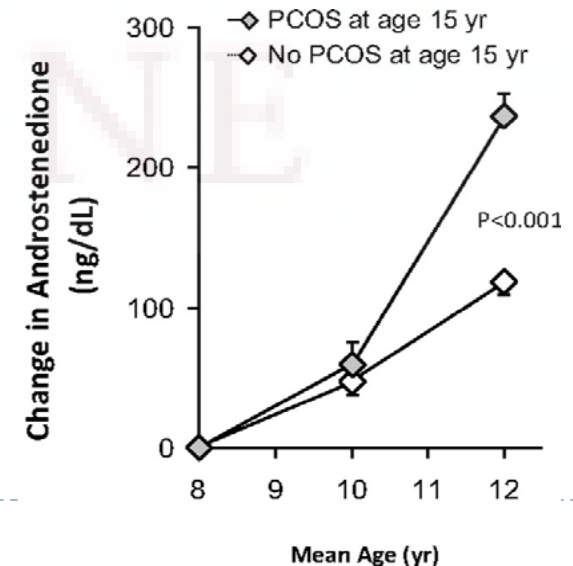
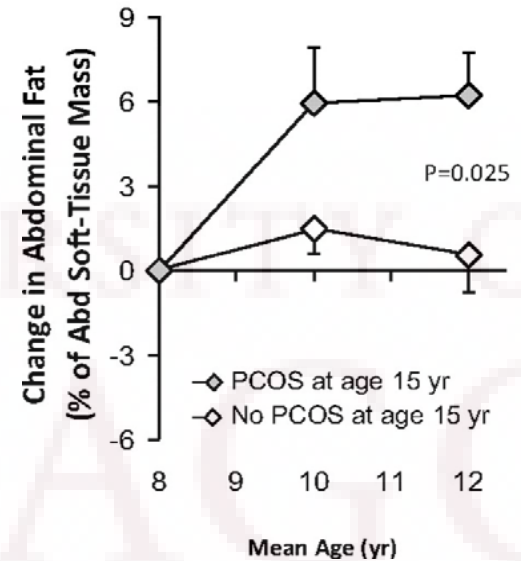
	Early metformin (0–4 yr)				Late metformin (5–6 yr)			
	0 yr ^b	7 yr	Δ 5–6 yr	Δ 6–7 yr	0 yr ^b	7 yr	Δ 5–6 yr	Δ 6–7 yr
Birth weight (g)		2386 ± 107				2471 ± 116		
Birth weight Z-score		-1.8 ± 0.1				-1.7 ± 0.1		
Age at PP (yr)		5.4 ± 0.3				6.1 ± 0.3		
Age at menarche (yr)		12.5 ± 0.2				11.4 ± 0.1 ^a		
Distance to target height (cm) ^f	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 ^o	0.2 ± 0.1 ^o
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 ^o	-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 ^o
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 ^o	-3.2 ± 1.2 ^o	0.8 ± 1.6 ^o
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 ^o	-0.8 ± 0.3 ^o	0.1 ± 0.4 ^o
SHBG (nmol/liter)	53 ± 5	36 ± 3	1 ± 2	2 ± 3	57 ± 4	29 ± 3	3 ± 3	-4 ± 1 ^o
DHEAS (μg/dl)	104 ± 10	233 ± 21	35 ± 8	11.3 ± 8.9	95 ± 9	276 ± 14 ^o	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 ^o	22.7 ± 16.4
Testosterone (ng/dl)	32 ± 3	41 ± 3	-5 ± 5	-4 ± 4	28 ± 3	47 ± 5	-25 ± 6 ^o	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 ^o	-5 ± 8	-1 ± 6
White blood cell count (10 ³ /μl)	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 ^o
Neutrophil count (10 ³ /μl)	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 ^o	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 ^o	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 ^o	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

Early vs Late Metformin Tx



Early vs Late Metformin Tx

	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



Summary

- ▶ Early Metformin showed reduction in PCOS in high-risk females (LBW-PP)
- ▶ These results are possibly attributed to reduction in adiposity

THE UNIVERSITY OF
CHICAGO
MEDICINE



References

- ▶ Shulman DI, Francis GL, Palmert MR, and Eugster EA. *Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development.* Pediatrics 2008; 121(4): e975-83.
 - ▶ Rosenfield RL, Bordini B, Yu C. *Comparison of detection of normal puberty in girls by a hormonal sleep test and a gonadotropin-releasing hormone agonist test.* J Clin Endocrinol Metab 2013; 98(4):1591-601.
 - ▶ Wit JM, Hero M, and Susan B. Nunez. *Aromatase inhibitors in pediatrics.* Nature Reviews Endocrinology 2012; 8, 135-47.
 - ▶ Ibáñez L, Díaz M, Sebastiani G, Marcos MV, López-Bermejo A, and de Zegher F. *Oral contraception vs insulin sensitization for 18 months in nonobese adolescents with androgen excess: posttreatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity, and menstrual regularity.* J Clin Endocrinol Metab 2013; 98(5):E902-7.
 - ▶ Ibáñez L, Lopez-Bermejo A, Diaz M, Marcos MV, and de Zegher F. *Early metformin therapy to delay menarche and augment height in girls with precocious pubarche.* Fertil Steril 2011;95(2):727-30.
 - ▶ Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, and de Zegher F. *Early metformin therapy (age 8-12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence.* J Clin Endocrinol Metab 2011;96(8):E1262-7.
-

