Secondary Amenorrhea and Clinical Hyperandrogenism in a 34-Year-Old Female: Polycystic Ovary Syndrome or Not?

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CASE DESCRIPTION

A 34-year-old female was referred to the endocrinology clinic for evaluation of secondary amenorrhea, hirsutism, and a possible diagnosis of polycystic ovary syndrome (PCOS). Menarche occurred at age 11, and menses were initially monthly. A combined oral contraceptive pill was taken for contraception and treatment of acne for a few months, until she developed a pulmonary embolism at age 21. After discontinuation of the combined oral contraceptive pill, menses became irregular. In her late twenties, she developed new hirsutism involving her chin and new, progressive hair loss involving the frontal and temporal scalp. At age 28, she was placed on norethindrone for contraception and became amenorrheic, which persisted 18 months after discontinuation. She denied clitoromegaly, acne, or deepening of her voice. She was prescribed spironolactone and metformin by her primary care physician for 3 years for presumptive PCOS despite worsening symptoms. In addition, she noted resistance to weight loss efforts with regular exercise and diet. She denied easy bruising and muscle weakness. Physical examination showed a body mass index (BMI) of 41 (obese), facial rounding, truncal adiposity, normal muscle mass, a few thin abdominal striae, and diminished volume of temporal and frontal scalp hair. Supraclavicular and dorsocervical fat pads and clitoromegaly were absent. Hemoglobin A1c values in the 3 years prior to presentation ranged from 5.1% to 5.4% (32–36 mmol/mol) [reference interval (RI): <5.7%; <38.8 mmol/mol], indicating good glycemic control. Thyroid stimulating hormone (TSH) values during the same time period ranged from 2.14 to 2.48 mcIU/mL (0.27–4.20), excluding thyroid dysfunction. The initial laboratory evaluation revealed the following: plasma follicle-stimulating hormone (FSH), <0.3 mIU/mL (RI: 3.5–12.5, follicular phase), luteinizing hormone (LH), 1.2 mIU/mL (RI: 2.4–12.6, follicular phase), 17β-estradiol, 67.8 pg/mL (RI: 12.4–233, follicular phase) [248.9 pmol/L (45.5–855.3)], 17α-hydroxyprogesterone (17-OHP), 285.1 ng/dL (RI: ≤206.0) [8.63 nmol/L (≤6.23)], dehydroepiandrosterone sulfate (DHEA-S), 155.0 mcg/dL (RI: 98.8–340.0) [4.2 mcmol/L (2.7–9.2)], sex hormone binding globulin (SHBG), 28 nmol/L (RI: 25–122), free testosterone, 67 pg/mL (1.3–9.2) [232.3 pmol/L (4.5–31.9)], total testosterone, 339 ng/dL (RI: 9–55) [11.8 nmol/L (0.3–1.9)], and anti-Müllerian hormone (AMH), 40.90 ng/mL (0.58–8.13) [292.1 pmol/L (4.1–58.1)]. Morning plasma adrenocorticotrophic hormone (ACTH) and cortisol measurements were 26.5 pg/mL (RI: 7.2–63.3) [5.8 pmol/L (1.6–13.9)] and 7.9 mcg/dL (RI: 4.8–19.5) [217.9 nmol/L (132.4–537.9)], respectively. Plasma prolactin was 13.1 ng/mL (5.3–37.8) [278.7 mcIU/mL (112.8–804.3]. Late-night salivary cortisol concentrations in samples collected at 11:00 PM on 2 successive days were 0.7 and 1.7 nmol/L (RI: <3.2). Plasma human chorionic gonadotropin (hCG) concentration was <0.2 mIU/mL (RI: <1.0). She subsequently underwent cosyntropin (adrenocorticotropic hormone) stimulation testing to evaluate for possible nonclassical congenital adrenal hyperplasia (NCCAH). Her baseline plasma cortisol was 8.1 mcg/dL (RI: 4.8–19.5) [223.4 nmol/L (132.4–537.9)], 30-minute cortisol was 25.8 mcg/dL (RI: >15.0) [711.7 nmol/L (>413.8)], and 60-minute cortisol was 29.0 mcg/dL (RI: >18.0) [800.0 nmol/L (>496.6)]. Corresponding 17-OHP values were 255.3 ng/dL at baseline, 399.2 ng/dL at 30 minutes, and 376.6 ng/dL at 60 minutes (baseline RI: ≤206.0, no RI for 30- and 60-

https://doi.org/10.1093/clinchem/hvae214

minute stimulated samples) [7.7, 12.1, 11.4 nmol/L (≤6.2)], excluding NCCAH. The full set of laboratory data is presented in Table 1.

QUESTIONS TO CONSIDER	
1.	What are the causes of secondary amenorrhea?
2.	What are the causes of hyperandrogenism?
3.	How is PCOS diagnosed?
4.	How can AMH be used in the evaluation of PCOS?
5.	What findings should prompt further evaluation in search of a non-PCOS cause of secondary amenorrhea?

Table 1. Initial laboratory results.

	Analyte	Concentration	Unit	RI
Serum/plasma	ACTH	26.5	pg/mL	7.2–63.3
(9:35 AM collection)	Cortisol	7.9	mcg/dL	4.8–19.5
	17-OHP	285.1	ng/dL	≤206.0
	DHEA-S	155.0	mcg/dL	98.8–340.0
	Prolactin	13.1	ng/mL	5.3–37.8
	FSH	< 0.3	mIU/mL	3.5–12.5 (follicular)
	LH	1.2	mIU/mL	2.4–12.6 (follicular)
	17β-Estradiol	67.8	pg/mL	12.4–233 (follicular)
	Total Testosterone	339	ng/dL	9–55
	Free Testosterone	67.0	pg/mL	1.3–9.2
	SHBG	28	nmol/L	25–122
	AMH	40.90	ng/mL	0.58–8.13
	hCG	<0.2	mIU/mL	< 1.0

Conversion factors: ACTH pg/mL x 0.2202 = pmol/L, cortisol mcg/dL x 27.6 = nmol/L, 17-OH progesterone ng/dL x 0.03 = nmol/L, DHEA-S mcg/dL x 0.027 = mcmol/L, 17β-estradiol pg/mL x 3.67 = pmol/L, total testosterone ng/dL x 0.035 = nmol/L, free testosterone pg/mL x 3.47 = pmol/L, AMH ng/mL x 7.14 = pmol/L.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the May 2025 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/71/5 and follow the link to the Clinical Case Study and Commentaries.

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