GYNECOLOGY

Increased anti-Mullerian hormone levels and ovarian size in a subgroup of women with functional hypothalamic amenorrhea: further identification of the link between polycystic ovary syndrome and functional hypothalamic amenorrhea

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BACKGROUND: Functional hypothalamic amenorrhea is a disorder characterized by cessation of menstrual cycles in the absence of organic disease. In most patients, it occurs in adult life after a stressful event and may be related to a condition of mild chronic energy deprivation. The endocrine pattern is characterized by low estrogen levels with an absent response to a progestogen challenge test and low-normal gonadotropin levels. A few studies have shown that some of these women may have some features of polycystic ovary syndrome; these features include an increased androgen response to gonadotropins, increased anti-Mullerian hormone levels, and altered ovarian morphology or increased ovarian size. These findings suggest a link between these 2 completely different disorders: functional hypothalamic amenorrhea and polycystic ovary syndrome. The importance of the possible coexistence of these disorders in some women is important for follow-up of these women and in their treatment if they desire to become pregnant.

OBJECTIVE: To determine whether a subgroup of well-characterized women with functional hypothalamic amenorrhea may have the coexistence of polycystic ovary syndrome.

STUDY DESIGN: Retrospective analysis of women with functional hypothalamic amenorrhea. Forty consecutive patients and 28 normal age-matched control patients were studied. Blood was obtained for serum anti-Mullerian hormone, androgens, and other hormone levels and all women had ovarian ultrasonographic measurements.

RESULTS: In the entire group of women with functional hypothalamic amenorrhea, anti-Mullerian hormone and ovarian volume were greater than in control patients. In 13 patients (32.5%), anti-Mullerian hormone was elevated (>4.7 ng/mL, levels consistent with polycystic ovary syndrome) and in this group, ovarian volume was significantly greater than in the remaining patients with functional hypothalamic amenorrhea. Four of the 13 women with functional hypothalamic amenorrhea who had elevated anti-Mullerian hormone levels (10%), also had ovarian volume $\geq$10 cc (consistent with polycystic ovarian syndrome). In these patients all studied androgens were in the upper normal range or slightly elevated despite low-normal gonadotropins; mean total testosterone was significantly greater than in the other patients with increased anti-Mullerian hormone values with normal ovarian size ($P<.05$.) Six other women with functional hypothalamic amenorrhea who had increased anti-Mullerian hormone also had isolated elevations of some androgen levels, but mean testosterone and ovarian size were normal.

CONCLUSIONS: As many as 10% of women with functional hypothalamic amenorrhea may have the coexistence of polycystic ovary syndrome. Because no signs or symptoms of this disorder were reported by these women before the appearance of the amenorrhea, it does not seem to be a coincidental relationship. The possibility that functional hypothalamic amenorrhea favors the appearance of polycystic ovary syndrome or more likely, that a mild (ovulatory) phenotype of polycystic ovary syndrome predisposes to the development of functional hypothalamic amenorrhea should be considered. Possible mechanisms are unclear and need to be investigated but may involve common vulnerabilities such as psychologic and mood disturbances.

Key words: anti-Mullerian hormone, functional hypothalamic amenorrhea, polycystic ovary syndrome

Functional hypothalamic amenorrhea (FHA) is a disorder characterized by dysfunction of the hypothalamic–pituitary–ovarian axis, leading to anovulation and cessation of menstrual cycles in the absence of organic disease.[1,2] In most instances, FHA occurs in adult life after a stressful event and may be related to a condition of mild chronic energy deprivation from excess energy expenditure, stress, and/or insufficient nutritional intake.[1-4] In many cases, there is no obvious reason found, and the FHA is considered idiopathic.

The endocrine pattern is characterized by low estrogen levels with an absent response to a progestogen challenge test and low–normal gonadotropin levels.[1,2] It has been suggested that increased cortisol, decreased kisspeptin, and low leptin levels may participate in the pathogenesis of this functional form of hypogonadotropic hypogonadism.[5,6]

It is not generally appreciated that some women with FHA may have features of polycystic ovary syndrome (PCOS) and that these disorders may coexist. It has been reported that some patients with FHA may have subtle increases in serum androgens during gonadotropin administration, similar to the response seen in women with PCOS, and in addition may have ovarian morphology similar to women with

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PCOS.[7] Similar studies have also reported an evolving picture of PCOS in women with FHA who were using pulsatile gonadotrophin-releasing hormone therapy.[8] We also have observed that some women with FHA exhibit increased androgen responses to controlled ovarian stimulation[9] and in long-term follow-up of the women described have found that some of these women developed features of PCOS as recovery of the hypothalamic–pituitary–ovarian axis occurred.[9]

Some studies have reported normal levels of serum anti-Mullerian hormone (AMH) in FHA,[10] but in most studies, serum AMH has been reported to be increased.[11,12] Increased AMH levels have been considered to be an important diagnostic marker for the altered ovarian morphology in women with PCOS.[13-15] Further confusing the picture in FHA, altered cystic morphology (not characteristic of polycystic ovaries) has been reported, which has been described to be multicystic or multifollicular, which may or may not result in slightly enlarged ovaries, but usually is not confused with polycystic ovaries.[16,17] In 1 report, as many as 41% of patients with FHA were reported to have enlarged ovaries (>10 cc).[17]

In this study, we wished to further characterize the possible relationship between FHA and PCOS and to estimate how frequently the coexistence may occur. In the hypoestrogenic state of FHA, we used serum AMH and ovarian parameters on ultrasound as possible markers. In so doing, we hoped to provide further insight into the possible connection between FHA and PCOS. A retrospective analysis of women with well-characterized FHA was performed.

Materials and Methods

We wished to compare well-characterized patients with FHA with a normal, age-matched control population and then determine features of these women with FHA (namely AMH levels and ovarian ultrasound findings) that resemble those of women with PCOS. Forty consecutive women with a diagnosis of FHA, aged 17–33 years (mean age 23.7 ± 5 years), were evaluated retrospectively. These patients were referred between 2012 and 2014 to the Endocrine Unit of the University of Palermo and the Department of Obstetrics and Gynecology of the University of Pisa, Pisa, Italy, because of secondary amenorrhea. All of these women reported fairly regular cycles before their complaint of amenorrhea. None of the women had severe weight loss or known eating disorders, and diagnosis of FHA was considered idiopathic. Some of these women had been treated previously with various therapies for amenorrhea but had not received any treatment for ≥3 months before evaluation in this study.

The diagnosis of FHA was based on the finding of secondary amenorrhea not associated with any organic disease, which was confirmed by the finding of hypoestrogenism (low estradiol levels <30 pg/mL; and no response to a progestogen challenge test). The women had normal levels of circulating prolactin and thyroid-stimulating hormone, and uterine disease was excluded by ultrasonography. In all patients magnetic resonance imaging of the brain was performed to exclude hypothalamic or pituitary disease.

For controls, we selected a group of 28 healthy women from Palermo who were age matched (mean age 23.4 ± 5 years) with the group of women with FHA. The controls were recruited from family members of hospital coworkers and had to have regular menses, no symptoms of hyperandrogenism (acne or hirsutism), and normal androgen levels. Normal menses were defined as cycles lasting 25–34 days. Patients and controls were all white Italian women.

All subjects underwent a complete history and physical examination, biochemical analyses, and transvaginal ultrasonography. Height and weight were recorded and body mass index (BMI) was calculated as kg/m^2. None of patients or controls was taking medications for at least 3 months before entering the study. The procedures were in accordance with the Helsinki Declaration of 1975 as revised in 1983 and this study was approved by the local Ethic Council.

Laboratory analyses

In all patients and controls serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone (T), dehydroepiandrosterone sulfate (DHEAS), androstenedione, cortisol, and AMH were evaluated. In controls, serum hormones were determined on days 3–5 of the cycle. Serum hormone levels were quantified by well-established methods that had been validated previously in our laboratories. LH, FSH, and estradiol were measured by traditional assays.[18] Total T concentrations were determined by the use of a competitive immunoassay (Johnson & Johnson - Ortho Clinical Inc., Rochester, NY). DHEAS concentrations were determined by the use of radioimmunoassay (Orion Diagnostics, Espoo, Finland). Androstenedione was measured by an enzyme-linked immunosorbent assay from DRG Instruments Gmbh, Marburg, Germany. AMH was measured by a commercial enzyme-linked immunosorbent assay, the AMH Gen II (Beckman Coulter, Brea, CA). The conversion of AMH in ng/mL to pmol/L requires that values be multiplied by 7.143. In all assays, intraassay and interassay coefficients of variation did not exceed 6% and 15%, respectively.

Biochemical hyperandrogenism was defined as serum T ≥60 ng/dL (≥2.08 nmol/L) and/or serum DHEAS ≥3 μg/mL (≥7.8 mmol/L) and/or serum androstenedione ≥3.2 ng/mL. These values for hyperandrogenism have been validated previously in adult women with the use of the previously described assays. Increased AMH levels were defined as serum AMH >4.7 ng/mL. This represented values above the upper 95% confidence intervals of our control population, and is the value shown by us (by ROC analyses)[15] and others by meta-analyses[14] to suggest the finding of polycystic ovaries.

Ovarian ultrasound

In all patients and in control subjects (between days 3 and 5 of the cycle), ovarian morphology was assessed by transvaginal ultrasound. In both centers, the same machine (MyLab 50 Xvision;

TABLE 1
Some clinical and hormonal characters of 40 patients with FHA compared with 28 normal ovulatory women of similar age

	Age, y	BMI, kg/m^2	LH, mIU/mL	FSH, mIU/mL	E2, pg/mL	Cortisol, ng/mL	Ovarian size, cc
FHA, n = 40	23.7 ± 5.4	19.6 ± 2.4	2.1 ± 1.4	5.6 ± 2.2	22 ± 8	16.1 ± 4.2	6.1 ± 3
Ovulatory controls, n = 28	23.4 ± 5	23.1 ± 4	5.6 ± 1.5	5.4 ± 1.6	43 ± 15	15.8 ± 4	4.3 ± 2
	NS	$P < .001$	$P < .001$	NS	$P < .001$	NS	$P < .05$

BMI, body mass index; *E2*, estradiol; *FHA*, functional hypothalamic amenorrhea; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *NS*, not significant.
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Esaote SpA, Genoa, Italy) was used but transducer frequency changed from 4−6 mHz to 8−10 mHz over the time the subjects were assessed, and this varied at the 2 different centers.

Ovarian volume was reported in all patients and was calculated by the formula $\pi/6$ ($D_1 \times D_2 \times D_3$) where the dimensions (D) of length, width, and thickness were used. The size of both ovaries was assessed, and mean ovarian size was calculated. In no instance was there the need to repeat ovarian ultrasound because of the finding of a dominant follicle. Increased ovarian size was defined as an ovarian volume ≥8.8 cc, which represented the upper 95% confidence intervals of our control population and according to our own ROC analyses for the ultrasound diagnosis of polycystic ovaries.[15] We could not rely on follicular or antral follicle counts because of the variability of this measure over time and the use of 2 different ultrasound transducers.

The addition of a PCOS control group was not considered necessary and the criteria for normal androgens, AMH levels, and ovarian volume have been described previously in this article. Such data on well-characterized patients may be found in our recent paper.[15]

Statistical analyses

Statistical analyses were performed with the use of Statview 5.0 (SAS Institute, Cary, NC). Univariate analyses were performed with the unpaired *t* test for the numeric variables, whereas the differences in the prevalence for the nominal variables were analyzed by the χ^2 test. Group means were compared using analysis of variance with post hoc least squares means pairwise comparisons (after log transformation of the values). Correlations were analyzed by Pearson test. We took the position that for women with FHA to possibly have coexisting polycystic ovaries or PCOS, AMH had to be elevated as well as having an increased ovarian volume suggestive of PCOS. All results are expressed as mean ± SD.

Results

In Tables 1 and 2, the main clinical and hormonal data of patients with FHA are depicted. In comparison with normal control patients, the entire group of women with FHA had lower BMI; ($P < .001$) and lower LH and estradiol levels ($P < .001$) but greater AMH ($P < .05$) and androstenedione ($P < .01$) values and larger ovarian volumes ($P < .05$). FSH, T, DHEAS, cortisol, and thyroid hormone values were similar in the 2 groups. The difference in AMH values between controls and FHA remained significant ($P < .01$) after we controlled for BMI. None of the controls had increased ovarian volume (mean 4.3 ± 2 cc) or high AMH values (mean: 2.8 ± 1 ng/mL).

In the entire group of patients, AMH levels correlated significantly with ovarian volume ($r = 0.47$, $P < .01$) and with T ($r = 0.35$, $P < .05$) and DHEAS ($r = 0.34$, $P < .05$); however, there was no correlation between AMH and age, BMI, LH, FSH, estradiol, androstenedione, and cortisol.

Thirteen of the 40 women with FHA (32.5%) had elevated AMH levels. In Tables 3 and 4, the hormonal profiles and ovarian size of the subgroups of women with FHA with increased or normal AMH are compared. The 2 subgroups had similar hormone profiles but ovarian size was significantly greater in FHA patients with increased AMH values.

Of the 13 women with FHA who had increased levels of AMH, 4 had increased ovarian volume (mean 11 ± 1.3 cc), all exceeding the threshold values (our threshold of >8.8 cc or the more commonly used value of ≥10 cc) suggesting polycystic ovaries. The individual values for ovarian size were: 12.8, 10.4, 10.8, and 10 cc. The same 4 patients had serum androgens in the upper normal range or just exceeding it: T (60, 48, 50, and 60 ng/dL), androstenedione

TABLE 2
AMH values and androgen levels in 40 FHA patients and 28 ovulatory controls

	AMH, ng/mL	T, ng/dL	DHEAS, μg/mL	A, ng/mL
FHA	3.9 ± 2.7	38 ± 18	1.9±1	2.9 ± 1.1
Ovulatory controls	2.8 ± 1	31 ± 13	1.9 ± 0.6	2.1 ± 0.5
	$P < .05$	NS	NS	$P < .01$

A, androstenedione; *AMH*, anti-Mullerian hormone; *DHEAS*, dehydroepiandrosterone sulfate; *FHA*, functional hypothalamic amenorrhea; *NS*, not significant; *T*, testosterone.
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TABLE 3
Some clinical and endocrine characters of 2 subgroups of patients with FHA, divided by normal versus high AMH values

	Number	BMI, kg/m^2	Age, y	LH, mIU/mL	FSH, mIU/mL	Estradiol, pg/mL	Cortisol, ng/mL	Ovarian size, cc
Normal AMH values	27	19.5 ± 2.4	24.4 ± 5.6	2.1 ± 1.4	5.7 ± 2.3	23 ± 8.4	16.3 ± 4.6	5.4 ± 2.8
Increased AMH values	13	19.9 ± 2.8	22.3 ± 5	2.2 ± 1.6	5.2 ± 1.9	22 ± 9.7	15.6 ± 3.4	7.6 ± 2.6
		NS	NS	NS	NS	NS	NS	$P < .05$

AMH, anti-Mullerian hormone; *BMI*, body mass index; *FHA*, functional hypothalamic amenorrhea; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *NS*, not significant.
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(3.7, 2.8, 3.85, and 4 ng/mL), and DHEAS (3.1, 3.2, 3.8, 1.58 μg/mL). Although the small number of patients precluded a complete statistical analysis, serum total T was significantly greater in these FHA patients with increased AMH and ovarian size (55 ± 6 ng/dL) compared with the FHA patients with increased AMH and normal ovarian size (39 ± 17 ng/dL, $P < .05$) as well as those FHA patients with normal AMH values (35 ± 18 ng/dL, $P < .01$).

Six of the remaining 9 women with FHA with increased levels of AMH and normal ovarian size had some isolated elevations in individual androgen levels, but mean serum T was similar to controls and those FHA patients with normal AMH values. Interestingly, among women with FHA with increased levels of AMH, AMH values were not different when we compared patients with FHA who had increased ovarian size (7.8 ± 2 ng/mL) or normal ovarian size (7 ± 1.4 ng/mL). Of the 27 FHA patients with normal AMH values, only 1 had enlarged ovaries and an isolated increase in serum androstenedione.

Discussion

FHA is a relatively uncommon disorder that may have different etiologies but is characterized by amenorrhea, usually related to a life event and is associated with low estrogen status. It has been suggested that, in most patients, FHA may be the result of a psychologic disturbance and/or a mild chronic energy deficiency (low caloric intake or exaggerated exercise or a combination of both.[1-3] Consistent with this premise, our patients with FHA, although not reporting alterations in food assumption, had a body weight in the lower normal range and a mean body weight that was significantly lower than in the normal controls.

It has been appreciated previously that patients with FHA may have altered ovarian morphology (multifollicular or polycystic ovaries), although this has not been well characterized, as well as increased androgen responses to gonadotropins.[7-9,16,17] More recently, we have shown that some patients with FHA respond to controlled gonadotropin hyperstimulation in the same way as women who have PCOS.[9]

TABLE 4
Serum androgens in 2 subgroups of patients with FHA, divided by normal vs high AMH values

	AMH, ng/mL	T, ng/dL	DHEAS, μg/mL	A, ng/mL
Normal AMH values	2.5 ± 1.3	35 ± 18	1.7 ± 0.9	2.7 ± 1
Increased AMH values	7.2 ± 1.6	45 ± 14	2.4 ± 1.2	3.2 ± 1
Significance	$P < .001$	NS	NS	NS

Significant elevations in T were observed in 4 women with increased AMH values ($P < .05$).

AMH, anti-Mullerian hormone; *DHEAS*, dehydroepiandrosterone sulfate; *FHA*, functional hypothalamic amenorrhea; *NS*, not significant.
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Because levels of serum AMH reflect ovarian follicular morphology,[19] the level of AMH should be considered to be useful in the assessment of women with FHA. Previous studies have shown levels of serum AMH to be either increased[11,12] or normal in FHA.[10] Increased AMH levels have been considered to be a hallmark feature of PCOS,[13-15] a disorder characterized by hyperandrogenism and disordered early follicle development, which may have a genetic trait associated with its etiology.[20] Because women with FHA have amenorrhea, one of the cardinal features of PCOS (menstrual irregularity) cannot be assessed, thus we depended on androgen levels and ovarian morphology as the only findings to assist in the diagnosis of possible PCOS. Because androgen levels in the absence of gonadotropin stimulation would be expected to be normal or low, the diagnosis of PCOS in women with FHA is indeed challenging.

Our study found that 13 of 40 women with FHA (32.5%) have AMH levels that are consistent with levels observed in women with PCOS; however, because women with FHA may have altered follicular activity that is different from polycystic ovaries (multicystic or multifollicular ovaries) that could explain the elevated AMH levels, we focused mainly on those women with increased AMH levels who also had increased ovarian volume (at a size which is consistent with PCOS.) Four of the 40 women with FHA, or 10% of the group, had these findings. In these patients, androgen levels were mildly elevated (with most individual levels of total T, Androstenedione, and DHEAS at or above the normal threshold); however, the mean total T was significantly greater

compared with FHA patients with increased AMH levels but normal ovarian size and the FHA patients with normal AMH values. These 4 women also had ovarian volumes ≥10 cc.

Apart from these 4 women with FHA who had increased AMH and ovarian volume, another 6 with increased AMH had some individual androgen levels that were mildly elevated, yet mean total T and ovarian volumes were normal. It is not clear whether these women may ultimately fit into the FHA/PCOS picture as well, which would make the prevalence of PCOS with FHA greater than 10%. It is more probable, however, that in these patients with FHA, increased AMH reflects a disturbance in early follicular development leading to multicystic ovaries, but not a polycystic ovary.

Because no signs or symptoms of PCOS were reported from any of the women with FHA before the appearance of the amenorrhea, this is not likely to be a coincidental relationship. It is interesting to speculate, however, whether it is FHA that gives rise to features of PCOS, or the reverse, suggesting that some women with PCOS develop FHA. In that stress and adrenal activation often is associated with FHA, this scenario is reminiscent of the theory of exaggerated adrenarche in the pathogenesis of PCOS. We do not feel, however, that this is a likely explanation for our findings. Rather, it is more plausible the latter circumstance is operative, namely that women with the milder (ovulatory) phenotype of PCOS predisposes to the development of FHA, often before a firm diagnosis of PCOS is even made.

According to Rotterdam criteria for the diagnosis of PCOS, various phenotypes are possible. This includes women who have ovulatory cycles, with hyperandrogenism and polycystic ovaries on ultrasound, known as phenotype "C," and other phenotypes of PCOS that require irregular cycles, but with 1 phenotype, phenotype "D," which is not associated with increased androgen levels.[21] Thus, it is intriguing to speculate that women with phenotype "C" PCOS may be more vulnerable or susceptible to developing FHA, whereas other phenotypes may not be as vulnerable. This in turn may shed some light on the pathophysiology involved in ovulatory PCOS and the interaction of the hypothalamus and ovary in FHA which will need to be investigated further in subsequent studies.

It is impossible to know whether this association between PCOS and FHA depends on some specific genetic trait or on the involvement of some hypothalamic common mechanism. Some time ago we suggested that psychological stress and associated findings are prevalent in some women with PCOS, and may be involved in its pathophysiology.[22] Moreover we know that in women with PCOS, mood disorders such as depression are prevalent.[23,24] Thus, it is our contention that there is a link between FHA and PCOS, where the symptoms and signs of PCOS are masked at least temporarily. Furthermore, it is our view that the prevalence of this coexistence occurs approximately 10% of women with FHA, but may be greater, and that it is likely that women with phenotype "C" or ovulatory PCOS are most vulnerable. Further studies and prolonged follow-up of these patients are needed to understand the link between these apparently different disorders.

One of the shortcomings of this study is that we did not systematically obtain follicle counts with high-resolution ultrasound. This is because of the retrospective nature of the study and the fact that the diagnosis was made earlier with older technology, and the lack of appreciation at that time of the value of follicular counts.[25,26] Indeed, we have found that follicle counts, as a sole criterion, is the most sensitive parameter (above the value of serum AMH and ovarian volume) in making the ultrasound diagnosis of PCOS.[15] Another shortcoming of this study is that we used available steroid assays at the time for the androgen measurements. Routine measurements of T, particularly in the past, have not been sufficiently precise in measuring the lower levels in women. This study would have benefitted from a more precise method, such as gas or liquid chromatography/mass spectrometry, to differentiate the lower levels in controls and the different subjects with FHA.

Finally, although the knowledge of whether women with FHA have cryptic PCOS or may ultimately exhibit more symptomatology is of interest, on a clinical basis, these women should be treated not on the basis of a diagnosis but according to symptoms and findings. Our study also confirms that increased values of AMH are common in patients with FHA. ■

References

1. Perkins RB, Hall JE, Martin KA. Aetiology, previous menstrual function and patterns of neuro-endocrine disturbance as prognostic indicators in hypothalamic amenorrhoea. Hum Reprod 2001;16:2198-205.
2. Giles DE, Berga SL. Cognitive and psychiatric correlates of functional hypothalamic amenorrhea: a controlled comparison. Fertil Steril 1993;60:486-92.
3. Williams NI, Berga SL, Cameron JL. Synergism between psychosocial and metabolic stressors: impact on reproductive function in cynomolgous monkeys. Am J Physiol Endocrinol Metab 2007;293:E270-6.
4. Bullen BA, Skrinar GS, Beitins IZ, von Mering G, Turnbull BA, McArthur JW. Induction of menstrual disorders by strenuous exercise in untrained women. N Engl J Med 1985;312:349-53.
5. Miller KK, Parulekar MS, Schoenfeld E, et al. Decreased leptin levels in normal weight women with hypothalamic amenorrhea: the effects of body composition and nutritional intake. J Clin Endocrinol Metab 1998;83:2309-12.
6. Skirupskaitz K, George JT, Anderson RA. The kisspeptin-GnRH pathway in human reproductive health and disease. Human Reprod Update 2014;20:485-500.
7. Shoham Z, Conway CS, Patel A, Jacobs HS. Polycystic ovaries in patients with hypogonadotropic hypogonadism: similarity of ovarian response to gonadotropin stimulation in patients with polycystic ovarian syndrome. Fertil Steril 1992;58:37-45.
8. Schachter M, Balen AH, Patel A, Jacobs HS. Hypogonadotropic patients with ultrasonographically detected polycystic ovaries: endocrine response to pulsatile gonadotropin-releasing hormone. Gynecol Endocrinol 1996;10:327-35.
9. Wang JG, Lobo RA. The complex relationship between hypothalamic amenorrhea and polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:1394-7.
10. Luisi S, Ciani V, Podfigurna-Stopa A, et al. Serum anti-Müllerian hormone, inhibin B, and total inhibin levels in women with hypothalamic amenorrhea and anorexia nervosa. Gynecol Endocrinol 2012;28:34-8.

11. Robin G, Gallo C, Catteau-Jonard S, et al. Polycystic Ovary-Like Abnormalities (PCO-L) in women with functional hypothalamic amenorrhea. J Clin Endocrinol Metab 2012;97:4236-43.
12. Lie Fong S, Schipper I, Valkenburg O, de Jong FH, Visser JA, Laven JS. The role of anti-Müllerian hormone in the classification of anovulatory infertility. Eur J Obstet Gynecol Reprod Biol 2015;186:75-9.
13. Eilertsen TB, Vanky E, Carlsen SM. Anti-Mullerian hormone in the diagnosis of polycystic ovary syndrome: can morphologic description be replaced? Hum Reprod 2012;27:2494-502.
14. Iliodromiti S, Kelsey TW, Anderson RA, Nelson SM. Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data. Hum Reprod 2014;29:2536-43.
15. Carmina E, Campagna AM, Fruzzetti F, Lobo RA. AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome (PCOS) in different phenotypes. Endocr Pract 2016 [Epub ahead of print].
16. Adams J, Franks S, Polson DW, Mason HD, Abdulwahid N, Tucker M, Morris DV, Price J, Jacobs HS. Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotropin releasing hormone. Lancet 1985;2:8469-70.
17. Futterweit W, Yeh HC, Mechanick JI. Ultrasonographic study of ovaries of 19 women with weight loss-related hypothalamic oligoamenorrhea. Biomed Pharmacother 1988;42:279-83.
18. Guastella E, Longo RA, Carmina E. Clinical and endocrine characteristics of the main PCOS phenotypes. Fertil Steril 2010;94:2197-201.
19. Dewailly D, Andersen CY, Balen A, et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update 2014;20:370-85.
20. Welt CK, Duran JM. Genetics of polycystic ovary syndrome. Semin Reprod Med 2014;32:177-82.
21. Dewailly D, Catteau-Jonard S, Reyss AC, Leroy M, Pigny P. Oligoanovulation with polycystic ovaries but not overt hyperandrogenism. J Clin Endocrinol Metab 2006;91:3922-7.
22. Lobo RA, Granger LP, Paul WL, Goebelsmann U, Mishell DR Jr. Psychological stress and increases in urinary norepinephrine metabolites, platelet serotonin, and adrenal androgens in women with polycystic ovary syndrome. Am J Obstet Gynecol 1983;145:496-503.
23. Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol 2011;117:145-52.
24. Scaruffi E, Gambineri A, Cattaneo S, Turra J, Vettor R, Mioni R. Personality and psychiatric disorders in women affected by polycystic ovary syndrome. Front Endocrinol (Lausanne) 2014;5:185.
25. Christ JP, Willis AD, Brooks ED, et al. Follicle number, not assessments of the ovarian stroma, represents the best ultrasonographic marker of polycystic ovary syndrome. Fertil Steril 2014;101:280-7.
26. Dewailly D, Lujan M, Carmina E, et al. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2014;20:334-52.

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