CLINICAL ENDOCRINOLOGY

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Clinical and biochemical discriminants between functional hypothalamic amenorrhoea (FHA) and polycystic ovary syndrome (PCOS)

Maria Phylactou, Sophie A. Clarke, Bijal Patel, Caitlin Baggaley, Channa N. Jayasena, Tom W. Kelsey, Alexander N. Comninos, Waljit S. Dhillo, Ali Abbara

Dr Mahnaz Pejman Sani
Assistant Professor of Endocrinology and Metabolic Diseases
Endocrine and Metabolism Research Institute
Tehran University of Medical Sciences

Outlines

- Introduction
- History and examination
- Biochemical/radiological investigations
- Overlap between FHA and PCOS
- Conclusion

Question

18 A 22-year-old woman with a 4-year history of functional hypothalamic amenorrhea comes to clinic for follow-up. She has a history of excessive exercise and restricted eating. Her BMI at her initial visit was 17 kg/m^2, and she had low bone mineral density (Z-score at femoral neck = −2.2). She understands that her low bone mineral density is related to her nutrition and excessive exercise, as evaluation for secondary causes has been negative. Eighteen months ago, she decided to implement lifestyle changes by moderating her exercise and improving her nutrition. Her weight has increased, and her BMI is now 18.5 kg/m^2. She is pleased that she has been able to make these changes but is disappointed that her periods have not returned. She wonders whether something else is wrong.

Laboratory test results:

- hCG = <3.0 mIU/mL (<3.0 mIU/mL)
  (SI: <3.0 IU/L [<3.0 IU/L])
- TSH = 1.9 mIU/L (0.5-5.0 mIU/L)
- Prolactin = 15 ng/mL (4-30 ng/mL)
  (SI: 0.65 nmol/L [0.17-1.30 nmol/L])
- Estradiol = 110 pg/mL (10-180 pg/mL)
  (SI: 403.8 pmol/L [36.7-660.8 pmol/L])
- LH = 6.0 mIU/mL (1.0-18.0 mIU/mL)
  (SI: 6.0 IU/L [1.0-18.0 IU/L])
- FSH = 8.0 mIU/mL (2.0-12.0 mIU/mL)
  (SI: 8.0 IU/L [2.0-12.0 IU/L])
- Progesterone = 7.0 ng/mL (≤1.0 ng/mL)
  (SI: 22.3 nmol/L [≤3.2 nmol/L])

Which of the following should be recommended now?

A. Start transdermal 17β-estradiol patch with cyclic micronized progesterone
B. Start alendronate, 70 mg weekly
C. Start a low-dosage combined estrogen-progestin oral contraceptive
D. No treatment

Introduction

- Secondary oligo/amenorrhoea occurs in **3%–5%** of women of reproductive age
- The two commonest causes are polycystic ovary syndrome **(PCOS) (2%–13%)** and functional hypothalamic amenorrhoea **(FHA) (1%–2%)**
- In practice, differentiating these two common causes of menstrual disturbance is challenging
- Moreover, both are diagnoses of exclusion qualified by the prerequisite to exclude other causes of menstrual disturbance

Introduction

- **PCOS** is diagnosed by **the presence of at least 2** of hyperandrogenism, oligo/amenorrhoea and polycystic ovarian morphology on ultrasound (PCOM)

- **FHA**: menstrual cycle length persistently >45 days or amenorrhoea >3 months, history of weight loss, vigorous exercise or stress, and the presence of hypogonadotrophic hypo-oestrogenism (typically <184 pmol/L)

- **negative progestogen challenge test and normal MRI pituitary are also recommended to confirm FHA**

Introduction

- **FHA** including **anorexia nervosa (AN)** and the **'female athlete triad' (FAT)**

Anorexia nervosa

- restricted energy intake leading to low body weight (moderate severity AN has BMI < 17 kg/m2)
- disturbed self-body image
- intense fear of weight gain or lack of recognition of the seriousness of low body weight

amenorrhoea is present in up to **89%** of AN

Introduction

Female Athlete Triad' (FAT)

- Menstrual disturbance
- Insufficient energy availability (dietary energy minus energy expended through exercise)
- Reduced bone mineral density (BMD) (Z score <−1.0)

Overt signs of low energy availability in FAT include **BMI ≤ 17.5** kg/m2 or **<85%** of expected body weight

Introduction

➢ **polycystic ovarian morphology (PCOM)**

- PCO (80%–88%)
- Healthy women (20%–30%)
- FHA (30%–45%)

Thus, even the clinician with specialist expertise may be faced with diagnostic uncertainty in women presenting with oligo/amenorrhoea

History & Examination

Menstrual disturbance

- Women with FHA typically present with amenorrhoea, whereas oligomenorrhoea is more common in PCOS

- Thresholds for cycle length used to signify menstrual disturbance vary from 35,2 to 38,7 to 45 days

- **Oligomenorrhoea** defined by the number of cycles per year (4–9 cycles per year)

- **Amenorrhoea** is defined as absent menses for ≥3 months or ≤3 cycles per year

History & Examination

- Most (80%–90%) women with oligomenorrhoea have PCOS, as compared to only 40% of women with amenorrhoea.

- Menarche in women with PCOS can be early if BMI is high or late if BMI is low
- Menarche in women with FHA or FAT have a propensity to late

History & Examination

Body mass index (BMI)

- PCOS is more common and FHA less common with increasing BMI
  - 12% of PCOS have BMI 25–30 kg/m2
  - 49% of PCOS have BMI ≥ 30 kg/m2

- **BMI threshold** of **26.6 kg/m2** discriminated Chinese women with PCOS (n = 300) from controls (n = 110) with an area under the ROC (AUROC) curve of 0.78 (sensitivity: 54.5%; specificity:98%).

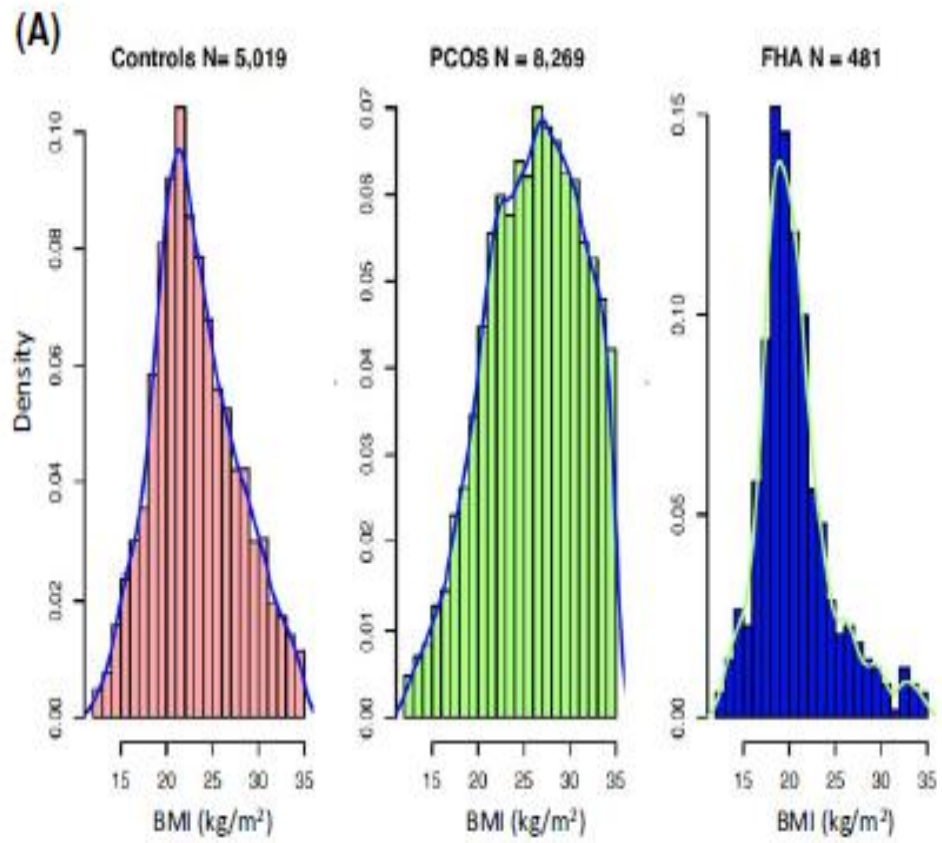
History & Examination

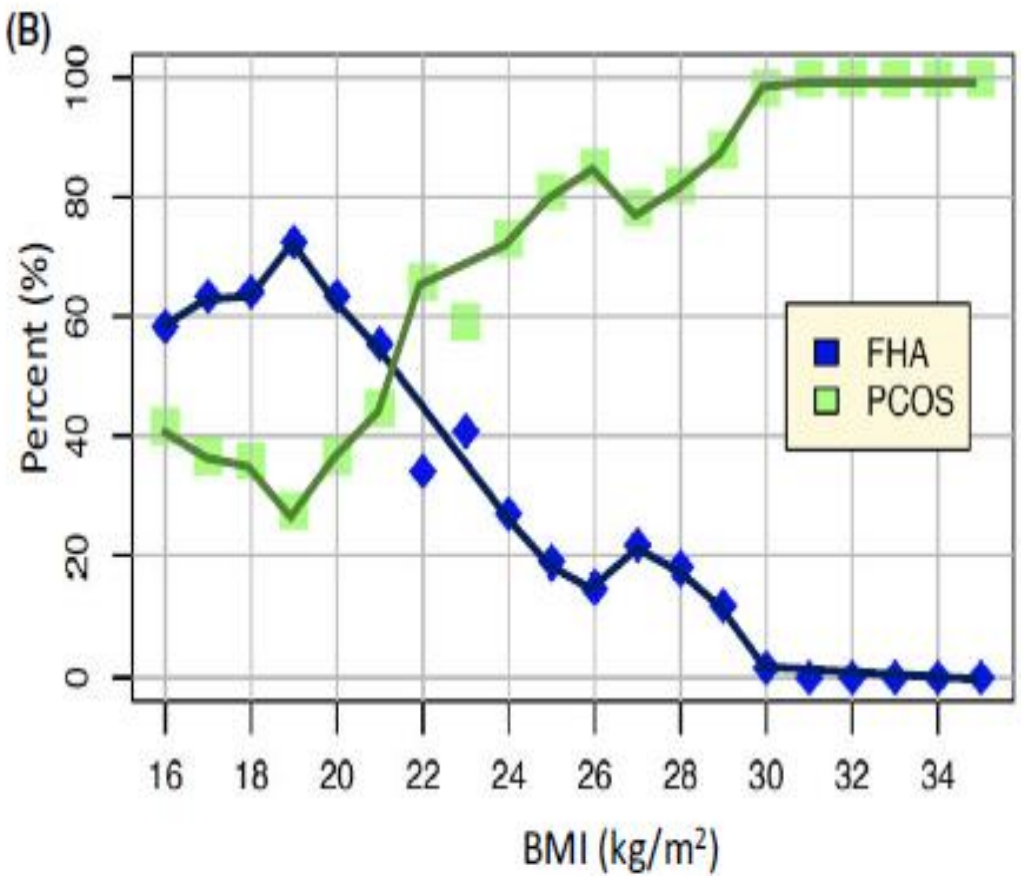
- FHA is due to one of, or a combination of low body weight, excessive exercise and psychological stress
- **One third of athletes** had amenorrhoea despite 'normal' BMI (21.3 ± 1.6 kg/m2)
- **Two thirds of women with AN** had amenorrhoea at a BMI between 17 and 18.9 kg/m2

- **Set point for body weight** at which menses are lost varies between individuals (generally BMI **< 24** kg/m2)
- **Recovery of menses** may require ~2 kg more than this set point and take up to 2 years after regain of normal body weight

History & Examination

- Recovery of menstrual function was observed in 86% of adolescents with **AN** who reached ≥90% of their ideal body weight
- **FHA** is uncommon in overweight women
- **PCOS** and **FHA** can occur in women with low/normal BMI's
- Although some women with FHA have 'normal' BMIs, typically these are in the lower half of the reference range


(A)
Controls N= 5,019
PCOS N = 8,269
FHA N = 481
Density
BMI (kg/m²)
BMI (kg/m²)
BMI (kg/m²)


(B)
Percent (%)
FHA
PCOS
BMI (kg/m²)

History & Examination

Body composition

- Body fat percentage is higher in lean PCOS than in weight-matched controls **(android)**

Fat Distribution Index (FDI = upper body fat mass/lower body fat mass)

Android >1.1

Gynoid < 0.9

- women with FHA have lower body fat mass than BMI-matched controls with 18%–28% body fat required for resumption of menses

History & Examination

- women with PCOS are almost twice as likely to have central obesity with a pooled estimate of **54%**.

- waist circumference and waist-to-hip ratios did not differ between PCOS and healthy controls in a large well-conducted study

- Markers that correlate with body weight such as **ghrelin**, **amylin, orexin A and adiponectin** can provide additional discriminatory potential over knowledge of BMI alone

History & Examination

Bone mineral density (BMD)

- Women with **FHA** have **reduced BMD** for chronological age
  - Hypo-oestrogenism
  - Nutritional deficits
  - Endocrine abnormalities (↑cortisol /↓IGF-1 levels)

- **FHA** guidelines recommend that a DEXA scan be conducted in all women with amenorrhoea of at least 6 months duration

- In **FAT**, lumbar BMD was reduced with T scores between −0.88 and −2.1.26 Lumbar

History & Examination

Bone mineral density (BMD)

- BMD is marginally reduced in women with PCOS and BMI < 27 kg/m2 with a pooled mean difference of −0.07, with no difference when BMI ≥ 27 kg/m2

- **low BMD is more consistent with FHA than PCOS**

History & Examination

Energy expenditure

- Resting energy expenditure (REE) was unchanged in PCOS
- In **PCOS** with **insulin resistance** adjusted basic metabolic rate (ie REE at rest >12 h after eating) was reduced (1116 vs 1868 kcal/day)

- Post-prandial thermogenesis was reduced in both obese (45.4 kJ vs 86.5 kJ) and lean (79.4 kJ vs 89.9 kJ) PCOS
- **Amenorrhoeic athletes** had lower REE than normo-ovulatory athletes or sedentary controls

History & Examination

- In **AN** REE was lower than controls even after adjustment for BMI and fat-free mass
- In **AN** REE was associated with Triiodothyronine (T3) levels
- **weight regain coincided with increases in both T3 and REE**
- Women with **FHA** may have slightly lower fT3 than controls (3.1 vs 4.2 pmol/L)
- **PCOS** may also be associated with mild thyroid dysfunction

History & Examination

Psychological disorders

- In **FHA** Psychological stress is one of the main aetiological factors
- Women with FHA had more life events than those with PCOS (FHA 59.8%, PCOS 26.6%)
- specific personality traits such as higher levels of perfectionism
- Cognitive behavioural therapy (CBT) increases the chance of recovery in FHA (87.5% vs 25%)

History & Examination

Psychological disorders

- **Depression** is more common in PCOS, independently of BMI
- PCOS increased the odds of depression by 3.8-fold and anxiety by 5.6-fold
- CBT resulted in weight loss and improved quality-of-life scores in PCOS

History & Examination

Eating disorders

- Almost half of FHA had disordered eating behaviours including dieting, bulimia, food and overweight preoccupation compared with 11% of controls
- Eating disorders, especially binge-eating disorder, were more frequent in PCOS (11%) than controls (7.6%)
- Both women with FHA and PCOS may display bulimic traits
- Restrictive eating patterns are more typically associated with FHA

History & Examination

Genetic predisposition

- **PCOS** is genetically predisposed, with ~**70%** heritability in monozygotic twins versus 38% in dizygotic twins/sisters

- In **FHA**, (**13%**) women had heterozygous variants in genes encoding for GnRH neuronal function or migration

- There is also a high degree of heritability in eating disorders such as **AN** (5%–60% in twin studies), specifically in genes regulating metabolism

Discriminatory potential of parameters

Parameter	Controls	FHA	PCOS	Area under the ROC curve to differentiate FHA from PCOS	Optimal threshold to differentiate FHA from PCOS
Body mass index (kg/m^2)	21.2 (20.3 22.4)	19.2 (18.8, 20.0)	25.0 (24.4, 27.3)	98.3%	100% sensitivity and 88.9% specificity at BMI 21.2 kg/m^2 84.6% sensitivity and 100% specificity at BMI 23.7 kg/m^2
Resting energy expenditure (REE, kJ)	5786 (5304, 6643)	4300 (4300, 4300)	6519 (5297, 6796)	100%	4798 kJ (same threshold when only including BMI < 25 kg/m^2)
Luteinising hormone (LH, IU/L)	5.14 (3.69, 6.40)	2.10 (0.84, 3.22)	9.58 (7.50, 10.68)	100%	5.36 IU/L
Anti-Müllerian hormone (AMH, pmol/L)	20.4 (14.7, 24.0)	27.9 (27.0, 35.4)	53.6 (47.1, 66.4)	100%	41.3 pmol/L
Antral follicle count (AFC)	10 (7.3, 17.8)	16 (6.5 20.5)	24 (16.6, 36.0)	88.9%	100% sensitivity and 66.7% Specificity at AFC > 16.3 66.7% sensitivity and 100% Specificity at AFC > 22.3
Proportion with PCOM	24%	31.4%	87.5%	n/a	PCOM was associated with an increased odds of PCOS diagnosis by 9.6-fold (95%CI 6.2-14.8) compared to FHA

Discriminatory potential of parameters

Parameter	Controls	FHA	PCOS	Area under the ROC curve to differentiate FHA from PCOS	Optimal threshold to differentiate FHA from PCOS
Inhibin B (pg/ml)	88.5 (75.2, 96.5)	46.5 (45.0, 48.0)	105.5 (64.2, 140.1)	100%	50.1 pg/ml
Fasting glucose (mmol/L)	4.87 (4.50, 5.14)	3.95 (3.80, 4.10)	4.90 (4.74, 5.51)	100%	4.3 mmol/L
Fasting insulin (pmol/L)	54.3 (36.3, 93.3)	86.1 (84.5, 193.7)	48.7 (30.4, 63.5)	100%	74.5 pmol/L
SHBG (nmol/L)	67.4 (63.3, 71.4)	61.4 (60.0, 62.9)	45.3 (44.0, 46.7)	100%	53.3 nmol/L
Total testosterone (nmol/L)	1.11 (1.12, 1.20)	0.92 (0.78, 1.06)	1.81 (1.49, 2.94)	100%	1.26 nmol/L
Total testosterone (nmol/L) BMI < 25 kg/m^2 only	1.15 (1.13, 1.79)	0.92 (0.78, 1.06)	2.45 (1.50, 3.4)	100%	1.26 nmol/L
Basal morning cortisol (nmol/L)	203 (144, 233)	255 (210, 300)	236 (227, 245)	50%	100% sensitivity & 50% specificity at cortisol 219 nmol/L

Biochemical/Radiological

GnRH pulsatility

- Hypothalamic GnRH pulsatility is increased in PCOS and reduced in FHA
- In long-distance runners with secondary amenorrhoea LH pulse frequency was reduced from 8 to 15 pulses per 24 h in controls to 1–6 pulses.
- LH pulsatility is disrupted at an energy availability <30 kcal/kg

Biochemical/Radiological

GnRH pulsatility

- In **FHA** LH pulse amplitude was reduced from 2.9 iU/L in controls to 0.7 iU/L
- Although reduced LH pulsatility is considered a hallmark feature of FHA, in fact only 8% of 49 women with FHA were completely apulsatile
- Overall, 78% had low pulse frequency (<9 pulses per 24 h) and 43% had low pulse amplitude (<4 iU/L)
- Estradiol levels were lower in those with reduced LH pulse amplitude

Biochemical/Radiological

- Women with **PCOS** have an inherent abnormality in the GnRH pulse generator that is **independent of sex steroids** with **higher pulse frequency** than controls (~22–24 vs ~16 pulses per 24 h)

- **LH pulse frequency** is increased in all women with PCOS by~40% and reduced in 78% of women with FHA

- **LH pulse amplitude** is not increased in obese PCOS and reduced in only 43% of FHA

- **LH pulse frequency is likely to have greater discriminatory factor**

Biochemical/Radiological

GnRH test

- In **FHA** LH responses to GnRH correlated with basal LH levels
- LH rises after 50 µg GnRH were similar in FHA (3.1 ≫ 8.6 iU/L; n = 8) as in healthy women (3.9 ≫ 6.0 iU/L; n = 6).
- In **PCOS** Absolute LH rises after GnRH (2–20 µg) were two- to three fold greater (BMI 34.7 kg/m2; n = 13) than in healthy women (BMI 26.8 kg/m2, n = 13).
- LH rises after GnRH positively correlated with basal LH values but negatively with BMI

Biochemical/Radiological

GnRH test

- An **LH/FSH ratio** at 30 min after GnRH of >2.11 had a 78.5% sensitivity and 87.5% specificity for the diagnosis of **PCOS**

- The response to GnRH in PCOS did not differ by androgen status

Biochemical/Radiological

Basal gonadotrophin values

- **LH levels** were raised to >95th percentile of healthy women in 40%–60% of PCOS
- **An LH:FSH ratio** of **1.33** had an AUROC curve of 0.87 (95% CI 0.84–0.89) to distinguish PCOS from healthy controls
- **LH levels can better aid in distinguishing FHA and PCOS than FSH levels**

Biochemical/Radiological

Growth hormone axis

- Women with **FHA** had higher nocturnal growth hormone (GH) levels than eumenorrhoeic controls (5.21 ± 0.89 vs 3.06 ± 0.33 µg/L)
- Although 24-h GH values did not differ
- Reduced nutritional intake results in GH resistance ⇒ (↑GH and ↓ IGF1)

Biochemical/Radiological

Anti-Müllerian hormone (AMH)

- **AMH** is produced by granulosa cells of growing antral follicles in the ovary and thus levels correlate with total antral follicle count (AFC).
- AMH is increased in PCOS corresponding to the number of PCOS features and better predicts menstrual disturbance than AFC
- AMH threshold of 33.6 pmol/L to have 79.4% sensitivity and 82.8% specificity for PCOS diagnosis

Biochemical/Radiological

PCO morphology on ultrasound

- **PCOM** is a cardinal feature of PCOS; morphologically
- PCOM ovaries have a central stroma surrounded by peripherally located follicles
- increased follicle number per ovary (FNPO) without this typical peripheral follicular distribution has been described as multicystic ovarian morphology (**MCOM**).
- PCOM by FNPO is reported in 30%–45% of FHA and 20%–30% of healthy women

Biochemical/Radiological

PCO morphology on ultrasound

- Recently, the recommended threshold for FNPO to denote PCOM has increased **from 12 to 20** to reflect improved ultrasound resolution

- Of the remainder, 67% (306/529) qualified as PCOS using an FNPO threshold>12, compared with only 9% (101/529) if using a threshold of >20

Biochemical/Radiological

Inhibin-B

- Inhibin B is produced by granulosa cells and peaks during the follicular phase
- Inhibin B **negatively correlates** with **BMI** in both PCOS and healthy women
- Inhibin B levels are lower in FHA than controls

Biochemical/Radiological

Circulating kisspeptin levels

- Kisspeptin neurons regulate GnRH neuronal pulsatility
- kisspeptin levels ↑ in PCOS and ↓ in FHA
- circulating kisspeptin levels have an AUROC curve of **0.84 for PCOS diagnosis**

Biochemical/Radiological

Progesterone withdrawal test and endometrial thickness (ET)

- **FHA** is a low estradiol state, whereas estradiol is typically preserved in PCOS
- **Estradiol levels** were reported to be higher in amenorrhoeic women who had a withdrawal bleed after a course of progesterone (297.4 vs 135.8 pmol/L) with a **threshold** of **146.9 pmol/L** predicting those who bled
- **40%–57% of women with FHA** have a withdrawal bleed after progesterone withdrawal and the response does not always relate to estradiol levels

Biochemical/Radiological

Progesterone withdrawal test and endometrial thickness (ET)

- **Endometrial thickness** (ET) better predicts the response to progesterone withdrawal than estradiol level
- ET is higher in PCOS than controls both on cycle days 3–5 (4.8 vs 3.4 mm)97 and on days 6–10 (11.1 vs 6.2 mm)
- it is unclear that the progesterone withdrawal test provides any additional information over estimation of ET.

Biochemical/Radiological

Insulin resistance

- Women with PCOS have a three- to five-fold increased risk of impaired glucose tolerance (IGT), depending on ethnicity
- Both **glucose and basal/stimulated insulin levels** were higher in PCOS than weight/age-matched controls after oral glucose tolerance test (OGTT)
- In lean (BMI < 25 kg/m2) PCOS, **fasting plasma glucose** did not significantly differ from controls however, 2-h glucose after an OGTT and HOMA IR were increased

Biochemical/Radiological

Sex hormone–binding globulin (SHBG)

- Insulin inhibits hepatic SHBG synthesis ➡ hyperinsulinaemia is associated with reduced SHBG levels
- SHBG levels are lower in PCOS even accounting for BMI
- Free androgen index (FAI) is likely to better differentiate FHA and PCOS than unadjusted testosterone levels.

Biochemical/Radiological

Androgens

- Women with **lean PCOS** (BMI < 25 kg/m2) had higher median testosterone ,DHEAS ,androstenedione and FAI than lean controls
- Women with **AN** had ↓ testosterone levels ,but SHBG or DHEAS levels did not differ
- Women with **AN** ↓ 5-alpha-reductase activity, whereas women with **PCOS** ↑ 5-alpha-reductase activity

Biochemical/Radiological

Leptin

- Leptin levels correlate with fat mass ⇒ in ↑ PCOS and ↓ in FHA
- Leptin levels are highest at midnight and lowest in the morning
- Leptin was also higher in overweight (BMI > 23 kg/m2) than lean controls
- **In FHA**, each 1 kg/m2 BMI increase was associated with an 0.89 µg/ml elevation in leptin levels

Biochemical/Radiological

Cortisol

- In **FHA** cortisol levels were higher than healthy women, and normalized after recovery of menstrual cyclicity
- Although cortisol pulse frequency is unchanged, cortisol pulse amplitude is increased
- basal cortisol levels were elevated in both conditions, the cortisol response to CRH is ↓ in FHA but in ↑ PCOS and thus could have discriminatory potential.

Biochemical/Radiological

Insulin-like factor 3 (INSL3)

- INSL3 is produced by ovarian theca cells and the corpus luteum.
- INSL3 levels were higher in women with PCOS
- It is correlated with follicle number, LH levels, hirsutism and androgen levels in PCOS

Overlap Between FHA and PCOS

- Of 159 women with **FHA**, 36% also met criteria for PCOS (25% PCOM, 6.9% hyperandrogenism, 5% both).

- Of 122 women with FHA, 41 'suspected of having underlying PCOS, had higher LH (7.7 vs 3.1 iU/L), testosterone (1.9 vs 1.1 nmol/L) and lumbar T scores (−1.1 vs −1.9)

- women with 'FHA and PCOM' may have ovaries that are prone to producing androgens, but that this may be masked by the low LH levels that are characteristic of FHA. Thus, FHA predominates when both conditions co-exist; however in some women, PCOS may be revealed following restoration of body weight or gonadotropin therapy.

Functional Hypothalamic Amenorrhoea (FHA)

Amenorrhoea
Decreased Energy Availability
BMI <24 kg/m²
⬇ Androgens
⬇LH level and LH pulse frequency

⟷ ⬇ Basal insulin levels
⬇Cortisol response to CRH
⬇Endometrial thickness
⬇ Bone Mineral Density

⟷ SHBG
⬆ AMH

Polycystic Ovary Syndrome (PCOS)

Oligomenorrhoea more common than Amenorrhoea
Any BMI
⬆ Androgens
⬆LH level and LH pulse frequency

⬆ Basal and stimulated insulin levels
⬆Cortisol response to CRH
⬆Endometrial Thickness
⟷ Bone mineral density

⬇ SHBG
⬆⬆⬆ AMH

POTENTIAL MARKERS pending further data: INSL-3 IGF-1 kisspeptin inhibin-B 5-alpha reductase activity


Thank you
for your
attention