무월경의 처치**:** 시상하부성 무월경

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- Age 31
- Chief complaint: "irregular menstruation"
- Brief history
 - 평소 월경 규칙적
 - 내원 2년 전부터 체중 감소 (15kg) 후 월경 불규칙, 내원1년 전 마지막 월경
 - 간헐적으로 호르몬 사용
- Menstrual & reproductive history
 - MN: A 13
 - Cyclicity (+) q 30d, duration: 7d, , amount: larger
 - P: -0-, contact (+)
- Initial check
 - BP: 90/53
 - Ht: 163.7 cm, Wt: 31 kg, BMI=11.67



Hormone test • - LH: 1.3 mIU/ml (0-52.8) FSH: 0.5 mIU/ml (0.3-93.3) E2: ▼ 1 pg/ml (10-441) TSH: 2.16 uIU/ml (0.3-6.50) PRL: 8.6 ng/ml (3.6-18.9) Pelvis US • - Ut: 5.5x2.4 cm, EMT=1.7 mm DXA • - L1-4: 0.745 g/cm² (Z: -2.3) FN: 0.613 g/cm² (Z: -1.2) 0.642 g/cm² (Z: -1.8) TH:

Diagnosis: functional hypothalamic amenorrhea, d/t weight loss



- Management
 - progynova 2 mg/day + dydrogesterone 10 mg for 12 days/month
 - consultation for PSY (r/o anorexia or bulimia nervosa)



	Wt/BMI	L1-4 (Z)	FN (Z)	TH (Z)
Baseline	31/11.7	0.745 (-2.3)	0.613 (-1.2)	0.642 (-1.8)
1y9m	50.2/18.8	0.797 (-1.8)	0.635 (-1.1)	0.673 (-1.5)
3y2m	49.8/18.4	0.835 (-1.8)	0.620 (-1.1)	0.659 (-1.5)

	Wt/BMI	LH	FSH	E2	AMH
Baseline	31/11.7	1.3	0.5	▼1	
10m	45.3/14.4				12.35
1y4m	42.5/15.8	0.9	0.2	267	16.72
1y9m	50.2/18.8				5.82
2y2m		0.4	0.2	122	11.39
3y2m	49.8/18.4	0.3	0.3	97	10.86
4y6m	53.8/20.0	3.2	3.6	68	6.10



Functional hypothalamic amenorrhea (FHA)

- Form of chronic anovulation that is not due to identifiable organic causes
- "Functional" implies that correction or amelioration of causal behavioral factors will restore ovulatory ovarian function
- Three main types: stress, weight loss, exercise
- Proximate cause of the anovulation: a functional reduction in GnRH drive
 → results in LH and FSH levels insufficient to maintain full folliculogenesis and
 ovulatory ovarian function
- There may be a genetic predisposition for the development of FHA



Hormonal and other changes in FHA



Gordon CM, NEJM 2010



Functional hypothalamic amenorrhea

- Tight link between activation of the <u>hypothalamic-pituitary-adrenal (HPA)</u> <u>axis</u> and reduction in GnRH drive in those with FHA
 - acute nutritional deprivation activates the HPA axis and reduces LH pulsatility
- Given the <u>energetic expense</u> of reproduction, <u>metabolic factors</u> play a fundamental role in gating reproductive function
- <u>Psychosocial influences</u>, including externally imposed stressors and stressful attitudes toward commonplace conditions
 - also activate the HPA axis and alter the neuromodulatory cascade that modulates GnRH drive



Neural interactions between metabolic & reproductive fx



Navarro VM, Curr Opin Endocrinol Diabetes Obes 2013

삼성서울병원

Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline

[Strength of recommendations] 1: strong recommendation, "we recommend"

2: weak recommendation, "we suggest"

[Quality of evidence]

- : very low
- : low
 - : moderate
 - ●●● : high



- We recommend that clinicians evaluate patients for inpatient treatment who have FHA and severe bradycardia, hypotension, orthostasis, and/or electrolyte imbalance. (1|●●●)
- In adolescents and women with FHA, we recommend correcting the <u>energy imbalance</u> to improve hypothalamic—pituitary—ovarian (HPO) axis function; this often requires behavioral change. Options for improving energy balance include increased caloric consumption, and/or improved nutrition, and/or decreased exercise activity. This often requires weight gain. (1|●●●)



Energy imbalance

- Amenorrhea may persist for some time after the reversal of precipitating factors
 - weight gain needed for the restoration of menses maybe higher than the weight at which menses stopped
- At least 6 to 12 months of weight stabilization may be required for the resumption of menses
- In some cases, regular menses may never resume after weight stabilization, emphasizing the importance of psychological factors and stress



- In adolescents and women with FHA, we suggest <u>psychological support</u>, such as cognitive behavior therapy (CBT). (2|●●)
- We suggest against patients with FHA using OCPs for the sole purpose of regaining menses or improving BMD. (2|●●)
- In patients with FHA using OCPs for contraception, we suggest educating patients regarding the fact that OCPs may mask the return of spontaneous menses and that bone loss may continue, particularly if patients maintain an energy deficit. (2|●●)



Psychological support

Compared to eumenorrheic women,

- exhibit more dysfunctional attitudes
- have greater difficulty in coping with daily stresses
- tend to have more interpersonal dependence
- often have a history of psychiatric disorders and primary mood disorders

СВТ

- restores ovarian function
- alters metabolic function!



Effects of hormones on BMD in anorexia-ass. FHA

	Туре	Dur	N (age)	BMD
Seeman (1992)	OC	32 cyc	16(27.6)	↑ LS, \leftrightarrow FN
Golden (2002)	EE 20-35	12m	22(16.8)	\leftrightarrow LS, hip
Munoz (2002)	EE 50	12m	22(17.4)	\leftrightarrow LS
Gordon (2002)	EE 20	12m	61(14-28)	\leftrightarrow spine, TH
Grinspoon (2002)	EE 35	9m	60(18-38)	\leftrightarrow
Strokosch (2006)	EE 35	13 сус	112(11-17)	\leftrightarrow vs. control
Klibanski (1995)	CEE 0.625	18m	22(23.7)	↔ spine CT
Karlsson (2000)	CEE 0.3-625	4.3y	58(25-28)	↑ LS, FN



Effects of \uparrow calorie intake and weight on BMD in FHA

	Dur	N (age)	BMD
Compston (2006)	12m	26(13-20)	\leftrightarrow
Drinkwater (1986)	15.5m	7(26.7)	↑ LS
Bolton (2005)	69w	15(23)	↑ LS
Dominguez (2007)	2.2m	28(18-35)	↑ spine, hip
Viapiana (2007)	13w	55(25.2)	↑ LS,FN,hip



Bone

- Studies reported mean BMD changes, but not Z-scores, T-scores, or the incidence of fractures
 no published prospective studies of fracture risk with OCP treatment in FHA
- The lumbar, femoral neck, trochanteric region, Ward's triangle, and total body BMD demonstrated clinically <u>insignificant changes</u> over a median of 12 months in a pooled analysis
- Lack of clear benefit is likely related to the persistence of neuroendocrine concomitants, including hypercortisolism and decreased thyroid levels
 FHA is more than an isolated disruption of the HPO axis!



- We suggest short-term use of transdermal E2 therapy with cyclic oral progestin (not oral contraceptives or ethinyl E2) in adolescents and women who have not had return of menses after a reasonable trial of nutritional, psychological, and/or modified exercise intervention. (2)
- We suggest against using bisphosphonates, denosumab, testosterone, and leptin to improve BMD in adolescents and women with FHA.(2|●●)
- In rare adult FHA cases, we suggest that short-term use of recombinant parathyroid hormone 1-34 (rPTH) is an option in the setting of delayed fracture healing and very low BMD. (2)●)



JBMR

Physiologic Estrogen Replacement Increases Bone Density in Adolescent Girls With Anorexia Nervosa



Misra M, JBMR 2011



Remarks

- Clinicians may consider estrogen replacement if reasonable attempts to modify nutritional, psychological, and exercise-related variables are not successful in establishing menses.
- Bone outcomes may be compromised even after 6 to 12 months of amenorrhea, and thus clinicians may consider short-term hormone replacement therapy after 6 to 12 months of nutritional, psychological, and exercise-related interventions in those with low bone density and/or evidence of skeletal fragility.
- Of note, bone health may not be protected with E2 replacement therapy if nutritional factors/energy deficit continue.



In patients with FHA wishing to conceive, after a complete fertility workup, we suggest:

- treatment with pulsatile gonadotropin-releasing hormone (GnRH) as a first line, followed by gonadatropin therapy and induction of ovulation when GnRH is not available (2)●)
- cautious use of gonadotropin therapy. $(2| \bullet)$
- a trial of treatment with clomiphene citrate for ovulation induction if a woman has a sufficient endogenous estrogen level (2)●)



In patients with FHA wishing to conceive, after a complete fertility workup, we suggest:

- against the use of kisspeptin and leptin for treating infertility $(2| \bullet)$
- given that there is only a single, small study suggesting efficacy, but minimal potential for harm, clinicians can consider a trial of CBT in women with FHA who wish to conceive, as this treatment has the potential to restore ovulatory cycles and fertility without the need for medical intervention. (2|●●)



 We suggest that clinicians should only induce ovulation in women with FHA that have a body mass index (BMI) of at least 18.5 kg/m² and only after attempts to normalize energy balance, due to the increased risk for fetal loss, small-for-gestational-age babies, preterm labor, and delivery by Cesarean section for extreme low weight. (2|●●)



Management in FHA: Summary

- Weight gain and exercise reduction
- Psychological approaches
- Interventions to mitigate bone loss
- Treatment for infertility



Thank you for your attention!

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