

ENDO 2017

THE ENDOCRINE SOCIETY'S 99TH ANNUAL MEETING & EXPO

Functional Hypothalamic Amenorrhea

An Endocrine Society Clinical Practice Guideline

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Agenda

I. Introduction

- a) Reasons for Developing an FHA guideline
- b) Pathophysiology
- c) Controversy and gaps in evidence
- d) Case Study

II. The Scope of the Problem

- a) Children & Adolescents
- b) Adults
- c) Fertility options

III. Content Review and Summary

- a) Answer to Case Study

I. Introduction

Session Learning Objectives

1. Understand the **pathophysiology underlying FHA** and the evidence base for the new ES guideline on this topic
2. Outline the **diagnostic work-up**, including blood testing, imaging, and functional studies
3. Understand **medical complications** of FHA
4. Identify a **management plan** for adolescents and women with FHA
5. Identify **gaps in knowledge** for FHA that will move forward a future research agenda

Functional Hypothalamic Amenorrhea (FHA)

FHA:

- Form of chronic anovulation
 - Cannot identify organic cause
 - Diagnosis of exclusion

“Functional”:

- Implies correction of causal behavioral factor will restore ovulatory function

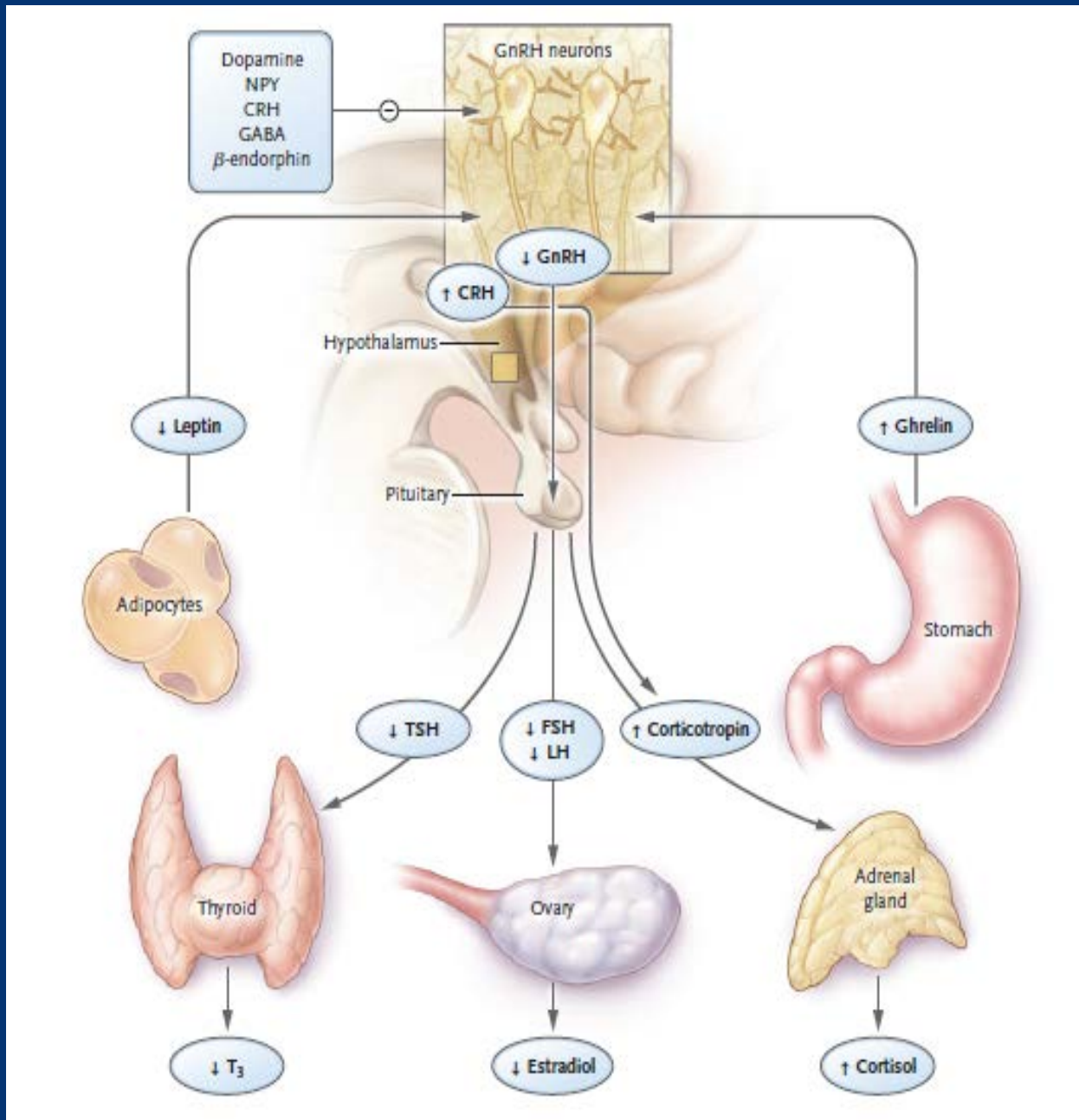
Anovulation:

- Due to functional reduction of GnRH drive, insufficient LH/FSH to maintain full folliculogenesis

Why Write a Guideline on FHA?

Controversial issue that crosses lifespan

- Opportunity for anticipatory guidance and prevention of future medical problems for **affected adolescents**
 - Optimize peak bone mass, prevent osteoporosis
 - Optimize fertility – adult women
- **Standardize work-up and treatment** for both teens and adults
 - Guidance regarding what constitutes thorough diagnostic evaluation, but avoid unnecessary testing
- **Dispel myths**
 - Irregular menses are not normal in an adolescent
 - Oral contraceptive pills in FHA do not confer bone protection



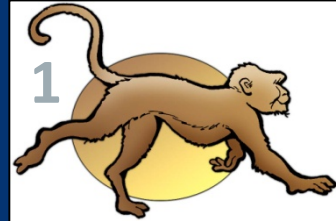
Decreased GnRH drive affects many organs and tissues

Not only issue of the hypothalamus....

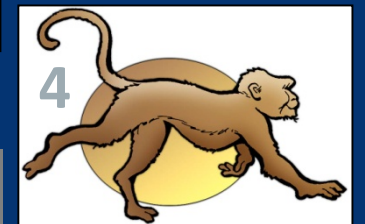
*Gordon CM,
N Engl J Med 2010*

The Monkey Pecking Order

Illustrates major source of stress-related physiological responses in females



Dominant – Social control



Subordinate – Lack of control

Thanks to Dr. Jay Kaplan, FHA Task Force, Wake Forest University

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Dominant females in the pecking order persistently harass subordinates, thereby causing elevated cortisol and ovarian disruption



Stress-Induced Ovarian Disruption: *Evidence for a Primate Continuum*

MONKEYS



Social Subordination

Luteal Impairment or Anovulation
(~45%)

Hypercortisolemia

Reversible Luteal Impairment

Environment: lack of control



**Precocious Bone Loss and
Atherosclerosis**

WOMEN



Inability to Cope

Functional Hypothalamic
Anovulatory Syndrome (~30%?)

Hypercortisolemia

Reversible Luteal Impairment

Environment: lack of control



**Chronic Disease
Risk?**

Good Ovulatory Function = Good Health



II. Scope of the Problem

Management of Adolescents with
Functional Hypothalamic Amenorrhea

GRADE Classification of Guideline Recommendations

| QUALITY OF EVIDENCE | | High Quality | Moderate Quality | Low Quality | Very Low Quality |
|--------------------------------|--|---|---|---|--|
| <i>Description of Evidence</i> | | <ul style="list-style-type: none"> Well-performed RCTs Very strong evidence from unbiased observational studies | <ul style="list-style-type: none"> RCTs with some limitations Strong evidence from unbiased observational studies | <ul style="list-style-type: none"> RCTs with serious flaws Some evidence from observational studies | <ul style="list-style-type: none"> Unsystematic clinical observations Very indirect evidence observational studies |
| STRENGTH OF RECOMMENDATION | Strong (1): “We recommend...” <i>Benefits clearly outweigh harms and burdens, or vice versa</i> | 1 ⊕⊕⊕⊕ | 1 ⊕⊕⊕○ | 1 ⊕⊕○○ | 1 ⊕○○○ |
| | Conditional (2): “We suggest...” <i>Benefits closely balanced with harms and burdens</i> | 2 ⊕⊕⊕⊕ | 2 ⊕⊕⊕○ | 2 ⊕⊕○○ | 2 ⊕○○○ |

Conditions of Low Energy Availability

Low energy availability (anorexia nervosa (AN), exercise induced amenorrhea) can impact many endocrine axes and lead to amenorrhea

What are we treating?

- Menstrual dysfunction (hypothalamic hypogonadism)
- Consequences of hypogonadism/other endocrine changes:
 - Low bone density (DXA, other methodologies), ↑ fracture risk
 - Cognitive and emotional outcomes
 - Fertility

Assessing Bone Loss in HA

2.7 We suggest that clinicians obtain a baseline BMD measurement by dual-energy X-ray absorptiometry (DXA) from any ***adolescent or woman*** with 6 or more months of amenorrhea, and that clinicians obtain it earlier in those patients with a history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility. (2|⊕⊕⊕○)

Management of FHA in Adolescents

Focus on:

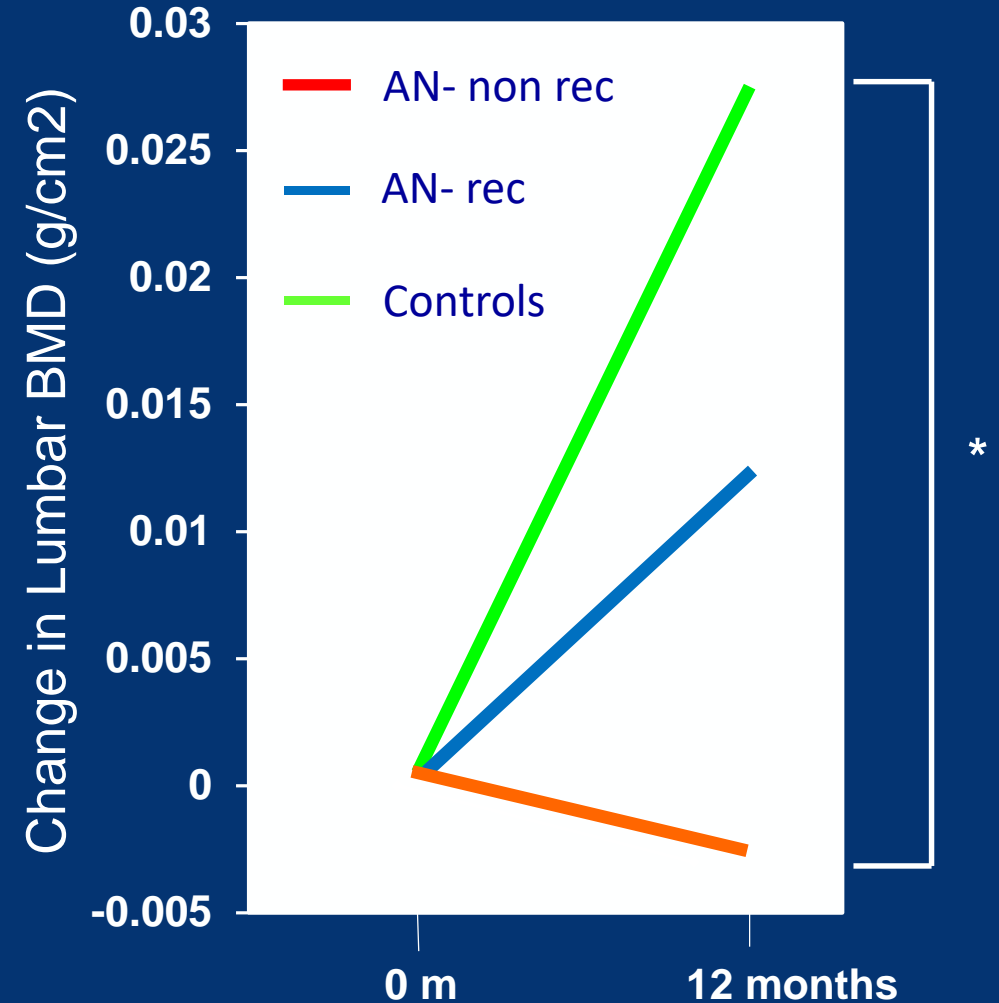
- Addressing low energy availability
- Hormone replacement strategies
- Other treatment strategies

Management: Nutritional Intervention

- Optimize energy availability (↑ body weight and fat mass)
 - ↑ energy intake
 - ↓ energy expenditure
- Benefits hypogonadism and its consequences
 - *Golden et al, 1992; Misra et al, 2006 and 2008; Chui et al, 2008; DiVasta et al, 2015*
- Low bone density: Consequent to body composition changes, hypogonadism, low IGF-I and leptin, high cortisol and PYY
 - Normalize or improve with optimization of energy availability
- Optimize calcium, vitamin D and other nutrients

Weight Gain, Menstrual Function and Bone Density

- Multidisciplinary team to work with patient and family to optimize energy status
 - CBT, family based therapies
- At menses recovery:
 - Body weight ~2 kg greater than that at which menses were lost
 - $91.6 \pm 9.1\%$ IBW
- May take 6-12 mo at $>90\%$ IBW before menses resume



Misra et al. JCEM 2008

Golden et al. Arch Pediatr Adolesc Med 1997

Recommendations: Correcting Energy Imbalance

3.2 In adolescents and women with FHA, we recommend correcting the energy imbalance to improve 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|⊕⊕⊕○)

3.3 In adolescents and women with FHA, we suggest psychological support, such as CBT. (2|⊕⊕○○)

- Challenging to implement: Yes
- Controversial: No

Management: Hormone Replacement (For bone outcomes)

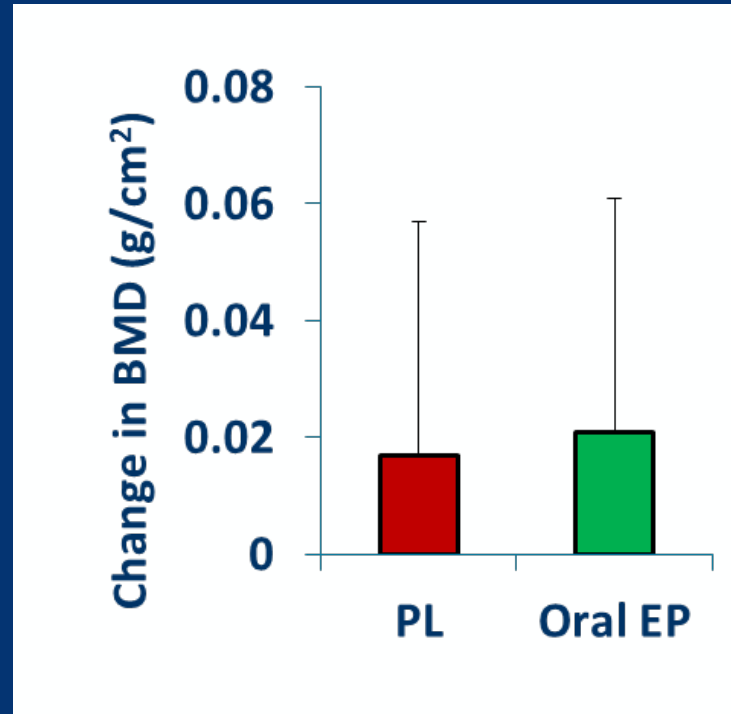
- Estrogen (several studies, one RCT in adolescents)
 - Anti-resorptive, possible bone anabolic effects
 - Positive effects on cognition and emotion
- DHEA (three studies in adolescents)
 - Anti-resorptive and bone anabolic effects
- Leptin (no studies in adolescents)
 - Bone anabolic effects
 - Stimulates GnRH pulsatility
- IGF-I (one short-term study in adolescents)
 - Bone anabolic effects
 - Positive effect on ovarian function

Estrogen Replacement (anti-resorptive): Oral

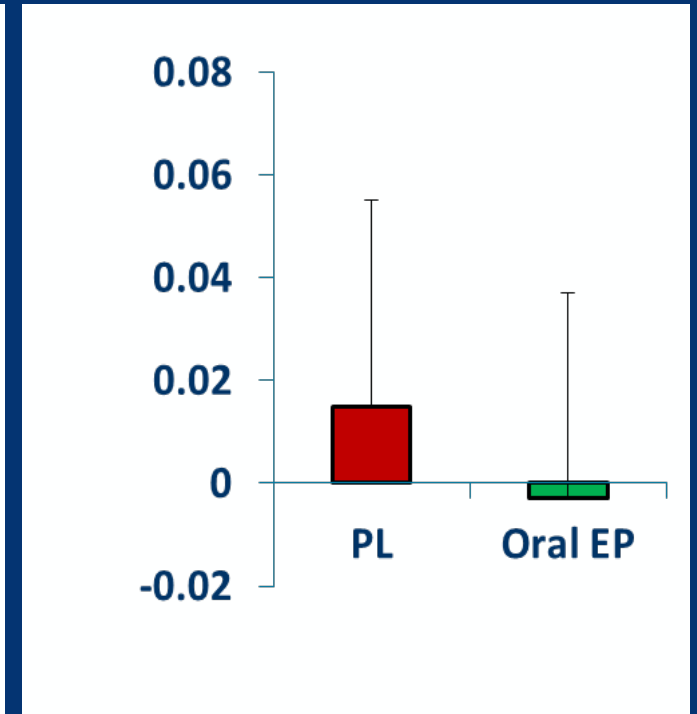
Oral E-P combination pills

- 12-m RCT of an E-P combination pill (an oral contraceptive) vs. placebo in adolescents with AN 12-18 yo
 - No \uparrow in BMD
- Small statistical effect in meta-analyses; minimal clinical effect
- Monthly menses may cause a false sense of security

Lumbar Spine



Total Hip



Strokosch et al. J Adol Health 2006

Suggestions: Estrogen Administration

3.4 We suggest against the use of OCPs in patients with FHA for the sole purpose of regaining menses or improving BMD. (2|⊕⊕○○)

3.5 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|⊕⊕○○)

- Challenging to implement: Yes
- Controversial: Not any more

Questions

Why is oral estrogen not more effective?

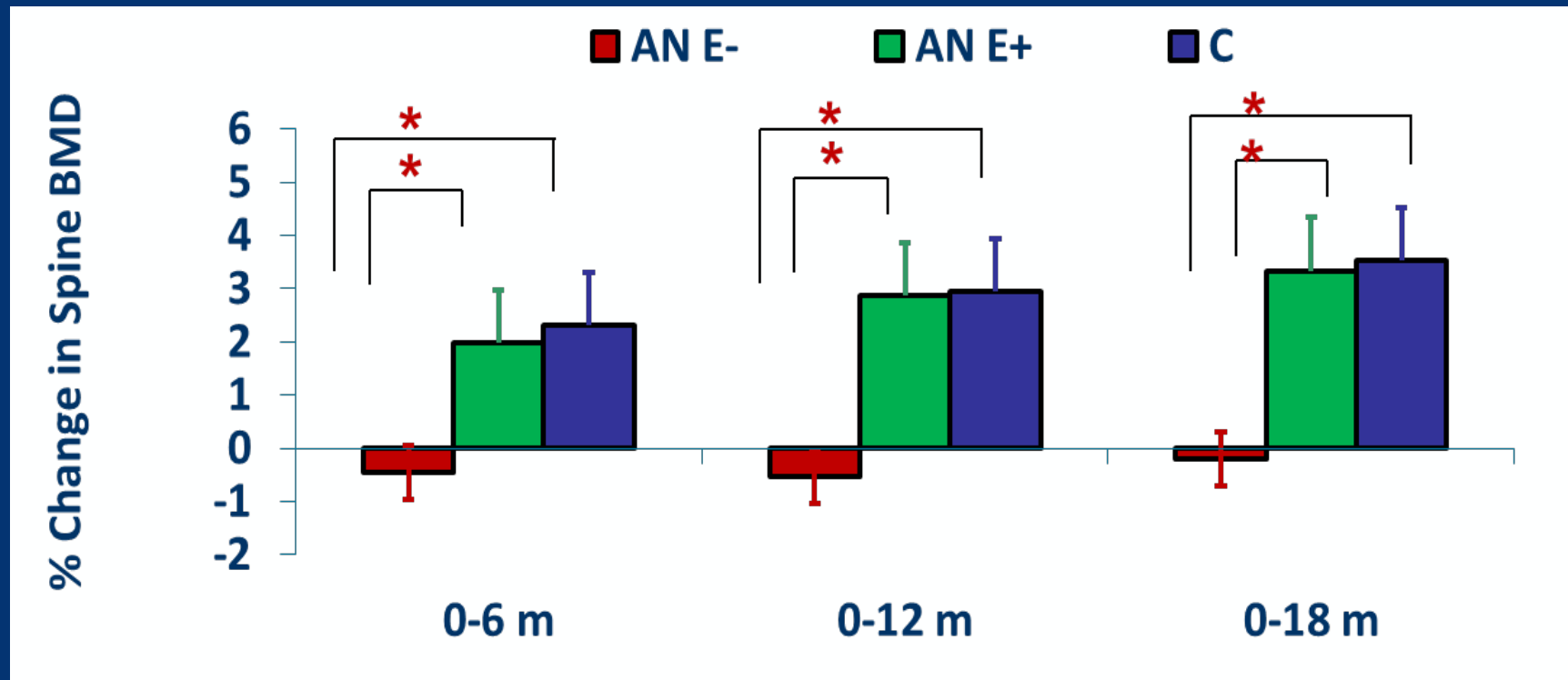
- Oral estrogen suppresses IGF-I
 - IGF-I ↑ bone formation
- Most oral preparations contain EE: non-physiologic form of estrogen (may be less effective for bone outcomes)

Are other estrogen administration strategies more effective?

- Transdermal estrogen (does not suppress IGF-I; 17-β E2)
- Oral 17-β E2 (no data)
- Combination with bone anabolic hormones (DHEA or rhIGF-I)

Estrogen Replacement: Transdermal

- 18-m RCT of transdermal estradiol (100 mcg) with cyclic oral progesterone vs. placebo in ~100 adolescents with AN 12-18 yo
 - ↑ Spine and hip BMD



Estrogen Replacement: Transdermal

- Improves trait anxiety measures in AN
 - *Misra et al. J Clin Psychiatr 2013*
- Prevents the increase in body dissatisfaction and anxiety observed in those who gain weight
 - *Misra et al. J Clin Psychiatr 2013*
- Improves verbal memory and executive function in normal weight athletes with amenorrhea
 - *Baskaran et al. J Clin Psychiatr 2017*

Suggestion: Estrogen Administration

3.6 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 6–12 months of a reasonable trial of nutritional, psychological and exercise intervention. (2|⊕○○○)

- Challenging to Implement: Possibly
- Controversial: No

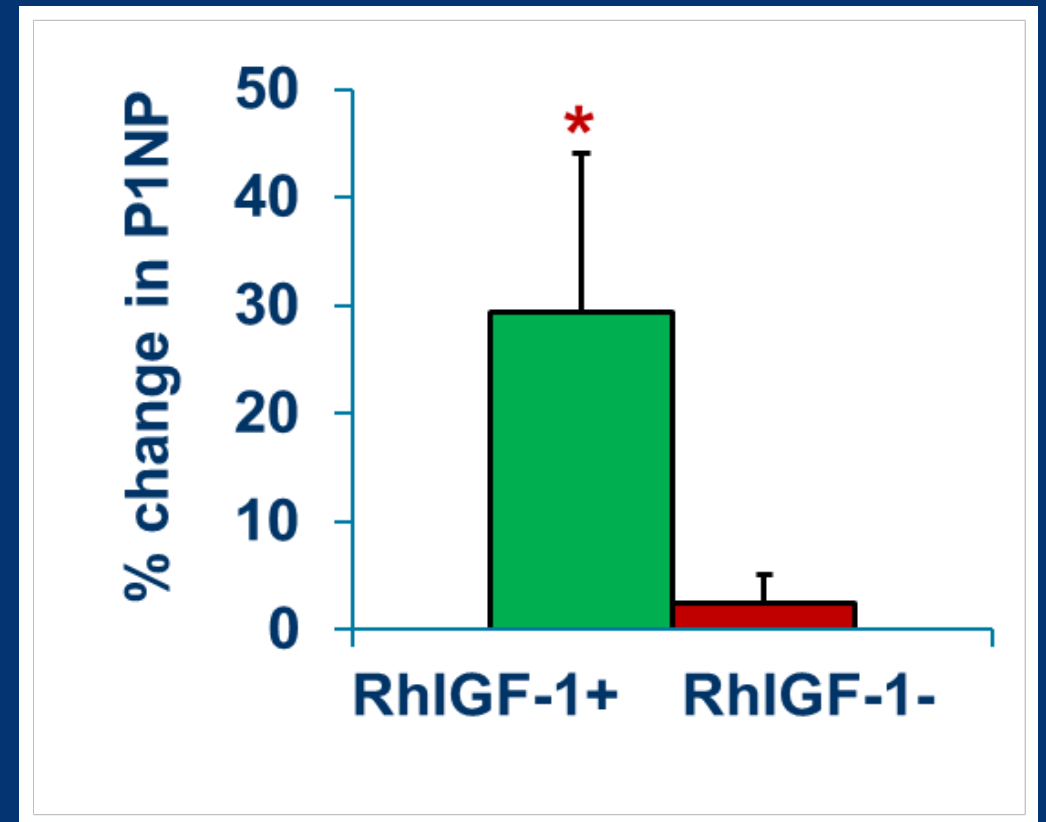
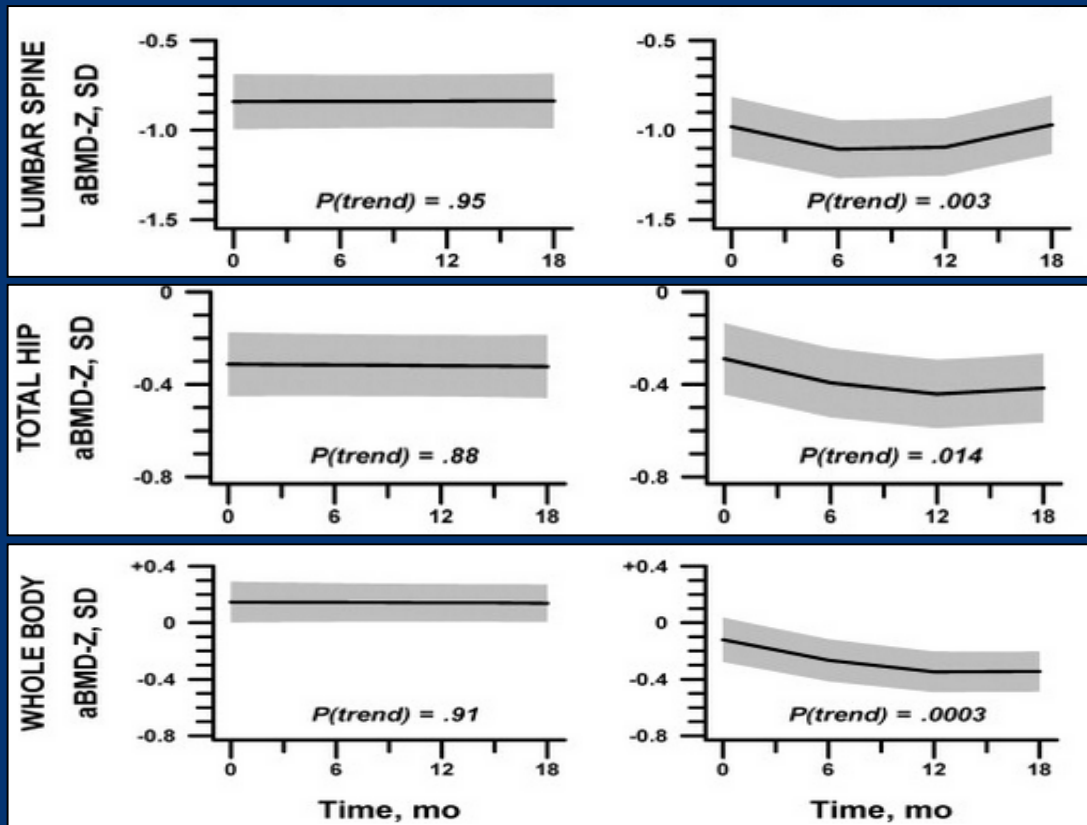
Estrogen with Replacement of Bone Anabolic Hormones (DHEA or IGF-I)

- 18-m RCT of oral E+P and DHEA (50 mg) vs. placebo
- Teens/women with AN 13-27 yo
DiVasta et al. Metabolism 2012

- RhIGF-I (30-40 mcg/kg bid) vs. no rhIGF-I
- Adolescent girls with AN 14-21 yo
Misra et al. Bone 2009

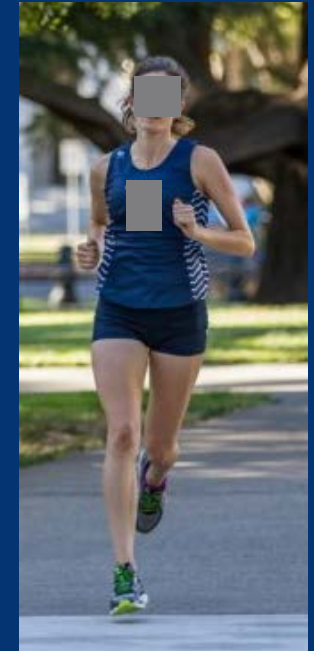
E+P/DHEA

PLACEBO



Case

- 17 year-old cross-country runner with groin/leg pain concerning for stress fracture
- Past Medical History
 - One prior tibial stress fracture and 1 metatarsal stress fracture
 - Three season runner, averaging 60 miles a week
 - Admits to restricting carbs to “stay at race weight”
 - Last period 11 months ago
 - Menarche at age 15 yr
- Hip radiographs and MRI negative, but Sports MD orders DXA because of risk factors
 - TBLH Z-score of -1.7 and LS Z-score of -1.8
 - *Remember DXA screening important in select adolescents...*



Case

- ✓ Referred to Sports Dietitian for detailed nutrition evaluation and counseling
- ✓ Referred for gait evaluation and physical therapy to optimize biomechanics
- ✓ Referred to Endocrinologist to address amenorrhea and low BMD

Case: History

- **ROS:** + constipation, diarrhea, and abdominal discomfort
- **Allergies:** NKDA or food allergies
- **Medications:** None
- **PMH:** 2 prior bone stress injuries
- **Fam Hx:** Mother's menarche - age 15, long-standing oligomenorrhea
- **Menstrual History:** menarche at age 15. 5 cycles the first year and then periods stopped
- **Social History:** No tobacco, alcohol, or drugs. Used to play soccer, basketball, and spring track, but transitioned into 3 season running athlete and increased training volume

Case: Physical Exam

- **Physical:** Ht 5'8", Wt 125 lbs, BMI 19.0 kg/m², HR 51, BP 110/70, non-orthostatic, Temp 98.1°C
- **Skin:** facial acne, Ferriman Gallwey score of 8/36
- **HEENT:** wnl
- **CV:** wnl
- **Lungs:** wnl
- **Abdomen:** wnl
- **Musculoskeletal:** wnl
- **Pelvic exam:** external and internal wnl

Case: Labs & Imaging

Labs:

- CMP- WNL except slightly elevated LFTs
- CBC- normal
- Iron studies- ferritin low, TIBC elevated
- Metabolic bone work-up negative except:
 - 25-hydroxyvitamin D 21.2 ng/mL
- Celiac screen negative
- LH + FSH low normal
- Estradiol- < 50 pg/mL
- Total and Free Testosterone- wnl
- TSH and Free T4- wnl
- Prolactin- wnl

Imaging:

- Pelvic US- wnl
- Brain MRI- wnl

Case Question

For this 17 yo, what is the best next step?

- A. Irregular menses are common in teenage athletes, so schedule a follow-up in 6 months
- B. Because estradiol has episodic secretion, recheck level in 2 weeks
- C. Begin bisphosphonate treatment to improve bone health
- D. Continue with multidisciplinary treatment and prescribe a progestin challenge

Case Answer

For this 17 yo, what is the best next step?

- A. Irregular menses are common in teenage athletes, so schedule a follow-up in 6 months
- B. Because estradiol has episodic secretion, recheck level in 2 weeks
- C. Begin bisphosphonate treatment to improve bone health
- D. Continue with multidisciplinary treatment and prescribe a progestin challenge

Treatment

- Optimization of calcium and vitamin D
- Regular visits with dietitian to improve energy availability and to achieve weight gain
- Frequent MD or NP visits for weight check and modifications of training
- Regular appointments with mental health professional for FBT/CBT
- Progestin challenge
- Appointment frequency depends on progress of patient
- May need to consider higher level of care

After 6 months of treatment, consider:

- Further exercise restriction
- Transdermal estrogen with oral progesterone

II. Scope of the Problem

Management of Adult Women with
Functional Hypothalamic Amenorrhea

Clinical Guideline Recommendation

3.2 In adolescents and women with FHA, we recommend correcting the energy imbalance 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|⊕⊕⊕○)

Nutritional Intervention for Reversal of Amenorrhea

Adequate Energy Availability (EA):

- Dietary intake minus energy expenditure normalized to fat free mass
 - For adult women, as well as adolescents (*Nattiv A et al Med Sci Sports Exer 2007*)
- Provides energy remaining for other body functions
- Inadequate EA associated with LH pulsatility disruption and other hormonal changes (*Loucks A et al JCEM 2003*)
- Weight gain through re-feeding and improved energy availability correlates with return of menses (*Dempfle A BMC Psychiatry 2003, Misra M JCEM 2008*)
- Increased EA through dietary modification or diet + exercise modification improved menstrual function in dancers and athletes (*Dueck CA Int J Sport Nutr 1996*), *Kopp-Wooddroffe SA Int J Sport Nutr 1999*, *Lagowska K J Int Soc Sports Nutri 2014*, *Mallison RJ J Int Soc Sports Nutri 2013*)

Evidence and Issues to Consider...

- One study suggested weight gain needed for return of menses was 2 kg (4.4 lb) higher than weight at which menses stopped (*Golden NH et al., Arch Pediat Adoles Med 1997*)
- At least 6-12 months of weight stabilization may be necessary for return of menses. Some may never return and many continue to have incipient eating disorders (*Warren MP J Soc Gynecol Investi 1994, Laughlin GA et al., JCEM 1994, Drew FL et al., J Clin Epidem, 1961*)
- Some with FHA and underlying PCOS may exhibit hyperandrogenism and irregular menses with weight gain and may not have return of regular menses (*Sum M, et al., Fert and Ster 2009*)
- First ovulation may occur prior to return of menses and sexually active women should be counseled accordingly

Psychological Support is Important

3.3 In adolescents and women with FHA, we suggest psychological support, such as cognitive behavior therapy (CBT). (2|⊕⊕○○)

- Women with FHA have been found to exhibit more dysfunctional attitudes, have greater difficulty in coping with daily stresses, and tend to have more interpersonal dependence than eumenorrheic women. They also more often have a history of psychiatric disorders and primary mood disorders than eumenorrheic women
 - Often resistant to weight gain
- CBT has been found to be useful and can help with stress reduction and return of menses

Management of Bone Loss in HA

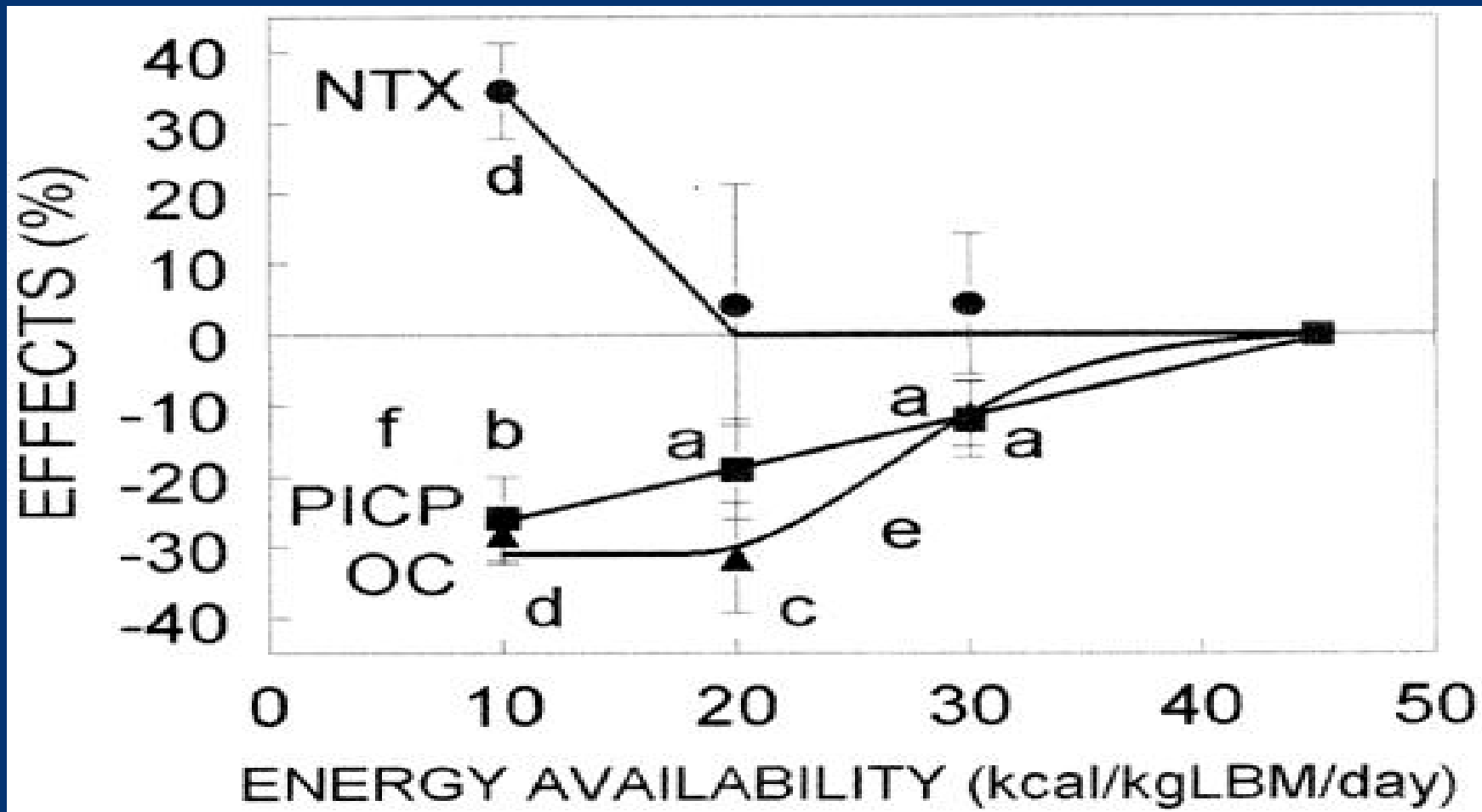
2.7 We suggest that clinicians obtain a baseline BMD measurement by dual-energy X-ray absorptiometry (DXA) from any ***adolescent or woman*** with 6 or more months of amenorrhea, and that clinicians obtain it earlier in those patients with a history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility. (2|⊕⊕⊕○)

2.9 This recommendation also applies to patients with FHA and underlying PCOS.

Nutritional Intervention for Bone

- Women with eating disorders are at high risk for bone loss and fractures
- Stress fractures are a common problem in athletes with amenorrhea
(Vestergaard P *Int J Eating Dis* 2002, Faje AT *Int J Eating Dis* 2014, Warren MP *NEJM* 1986)
- Low energy state in adult women leads to low bone formation with high resorption.
 - Uncoupling of bone turnover unique to nutritional deprivation in older adolescent or adult, can be reproduced with short-term starvation and reversed with improvement in energy status (Grinspoon et al *JCEM* 1999, Soyka et al *JCEM* 1999, Gordon et al *J Pediatr* 2002, Ilhe R et al *JBMR* 2004)
- Large (>4%) increases in BMD seen in as little as 2.2 months with improvement in energy status. BMD↑ present with or without return of menses. This is in comparison with all other Rx studied so far of 1-2%.
 - Without nutritional intervention, estrogen therapy or other treatment may fail most likely due to low bone formation (Dominguez J et al *Am J Clin Nutr* 2007)

Incremental Effects of Low Energy Availability on NTX, PICP and Osteocalcin After 5-day Nutritional Restriction in Normal Women



NTX - (●)
PICP - (■)
OC - (▲)

*Ihle R, Loucks A,
JBMR 2004*

Bone Density Changes in Patients with Anorexia Nervosa with 2.2 Months of Nutritional Rehabilitation. BMI at admission 16.1 ± 1.1

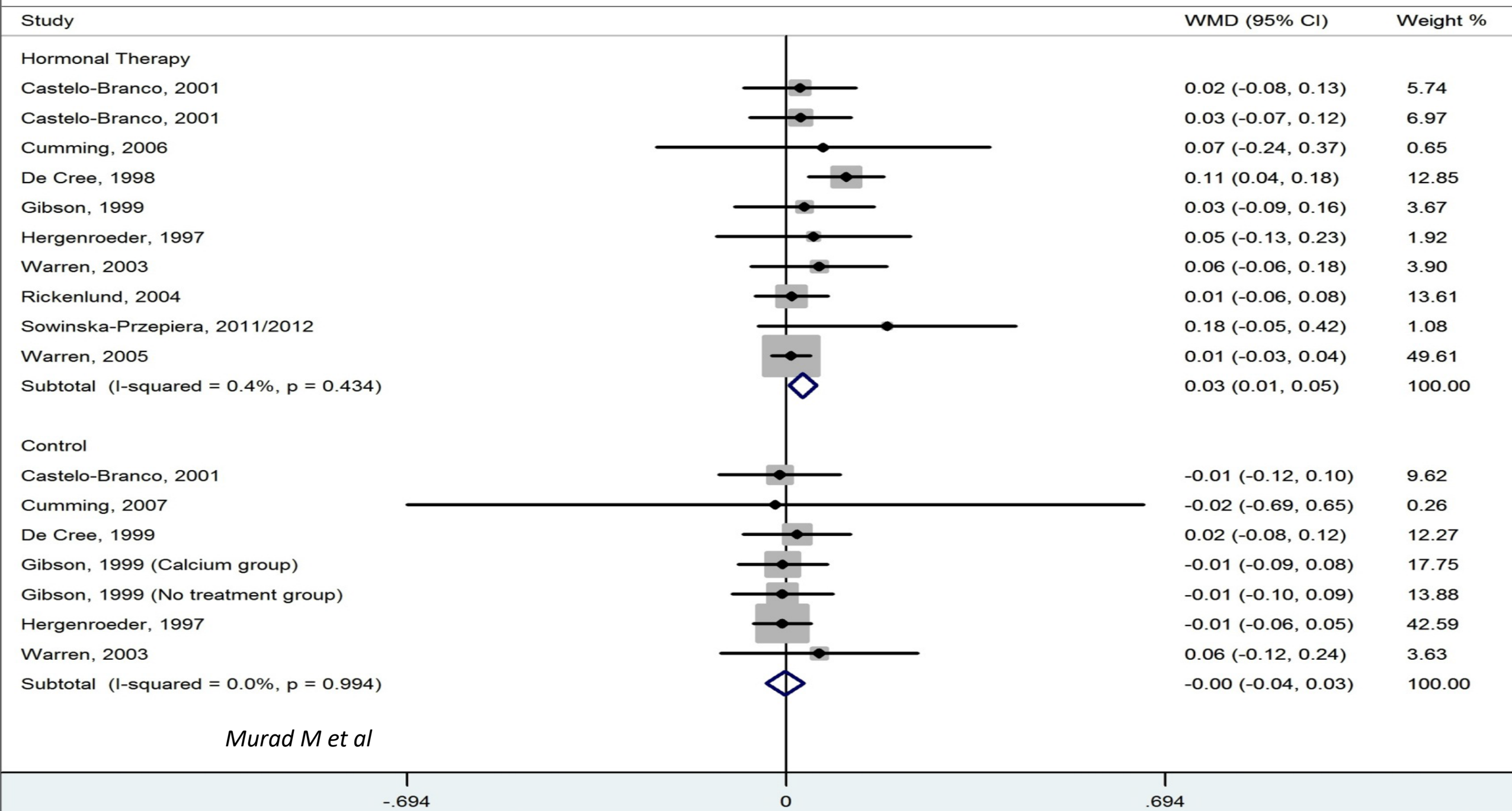
| | Amenorrheic at 90% IBW (n=16) | | | Regained Menses at 90% IBW (n=5) | | | Controls (n=6) |
|----------------------------|-------------------------------|---------------|------|----------------------------------|---------------|------|----------------|
| Bone | a. Admit Weight | b. 90% IBW | % ↑ | c. Admit Weight | d. 90% IBW | % ↑ | e. 90-100% IBW |
| Spine (g/cm ²) | 0.903 ± 0.144 | 0.941 ± 0.136 | 4.21 | 0.969 ± 0.177 | 0.996 ± 0.170 | 2.79 | 1.119 ± 0.063 |
| Hip (g/cm ²) | 0.922 ± 0.124 | 0.957 ± 0.112 | 3.80 | 0.971 ± 0.107 | 1.001 ± 0.107 | 3.09 | 1.066 ± 0.045 |
| Total (g/cm ²) | 1.055 ± 0.094 | 1.056 ± 0.084 | 0.10 | 1.099 ± 0.031 | 1.102 ± 0.037 | 0.30 | 1.126 ± 0.044 |

Dominguez J et al., Am J of Clin Nutri 2007

Other Interventions for Bone

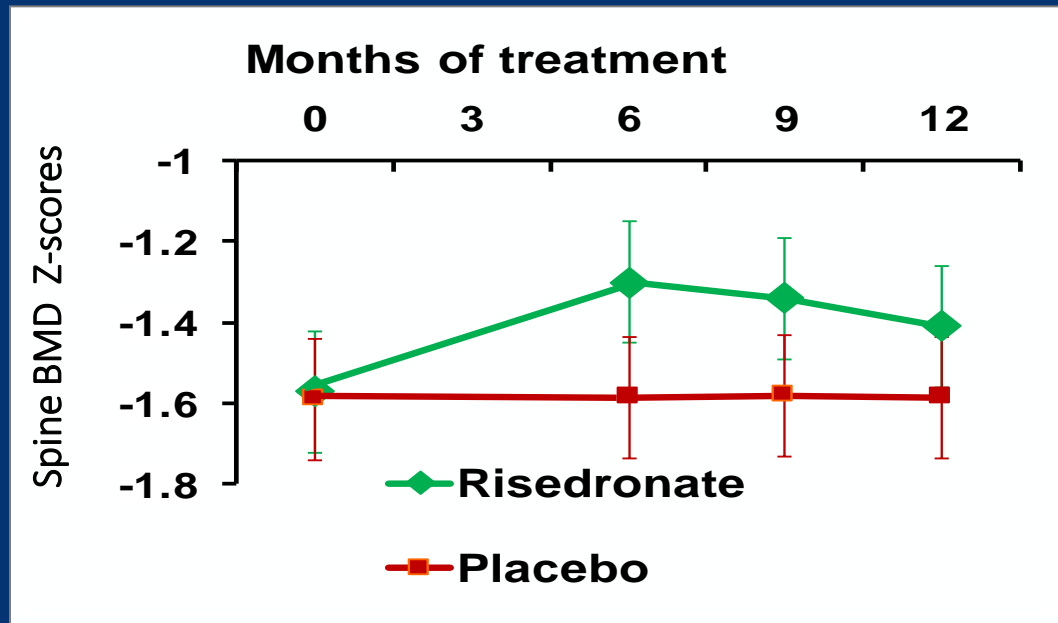
- Many patients will not follow behavioral changes necessary to improve nutrition and energy status
- Estrogen therapy (preference – transdermal) may be helpful in women who have had a reasonable trial of nutritional, psychological and modified exercise intervention
- Bisphosphonates are generally not recommended in young women as they are incorporated into bone for years and animal studies have shown fetal harm (*Djokanovic N et al., J Obstet Gynaecol Can 2008*)
- Testosterone +/- risedronate not effective (*Miller et al., JCEM 2011*)

Figure 2: Pooled difference in means of Lumbar Spine BMD before and after receiving Hormonal Therapy and Placebo/No Treatment

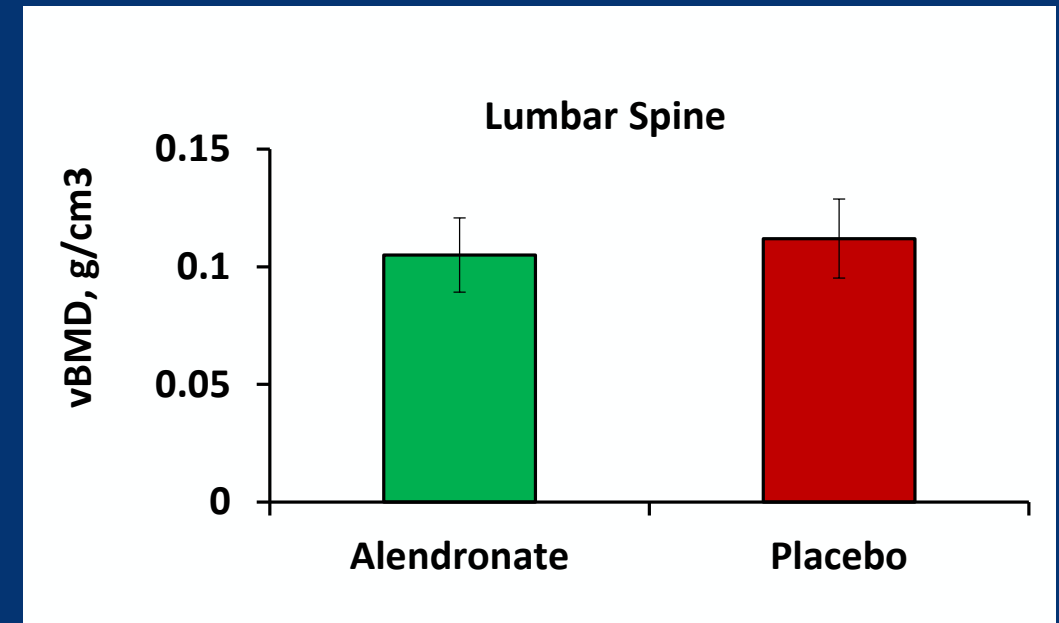


Other Treatment Modalities: Bisphosphonates

- Risedronate effective in adult AN (12m RCT)
- Spine and hip BMD Z-scores ↑ 3.2 & 1.9%



Miller et al JCEM 2011



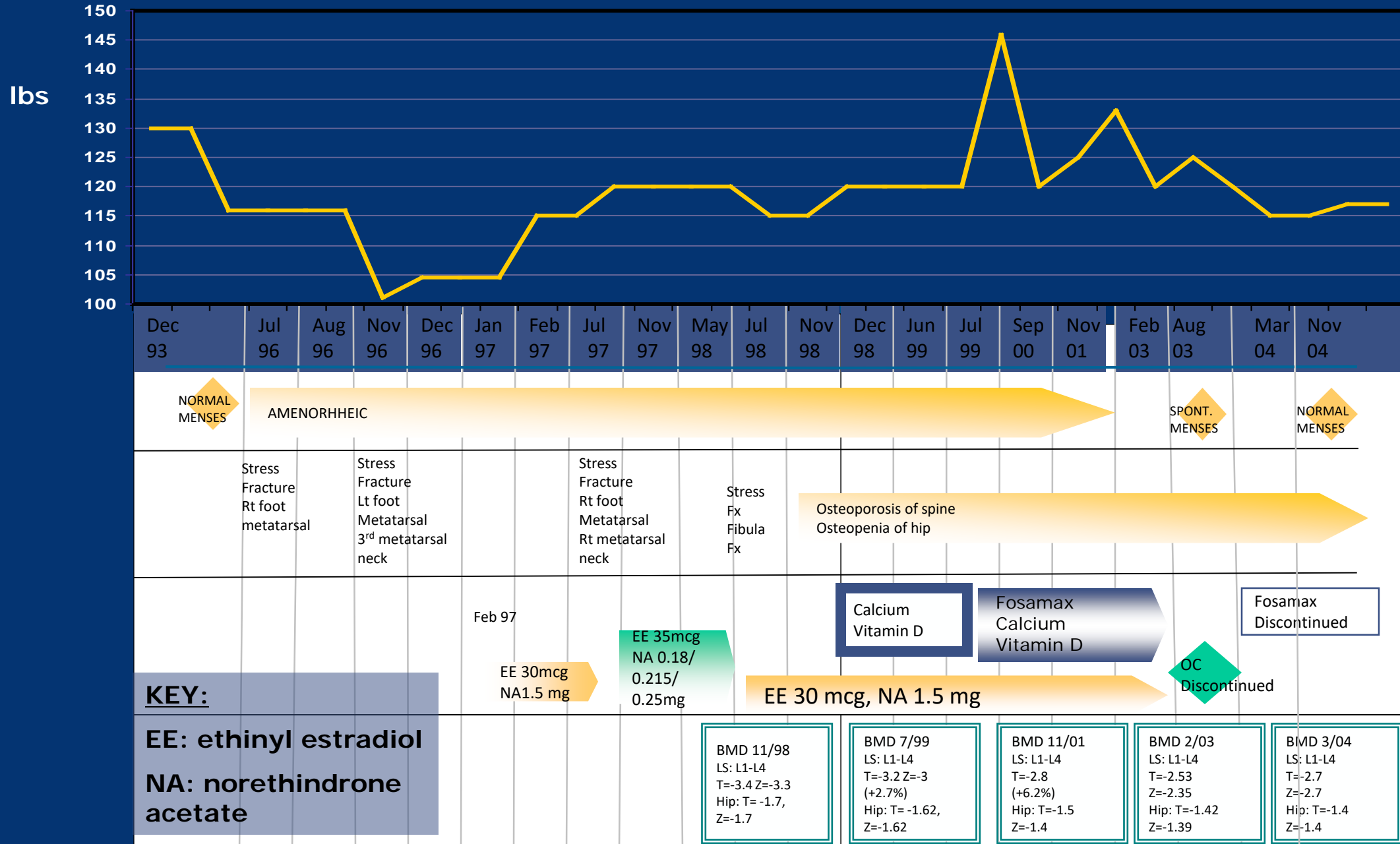
Golden et al. JCEM 2004

- Alendronate not effective in increasing spine BMD in adolescent AN 12-18 yo (12m RCT); small increases noted at the femoral neck
- Denosumab and teriparatide (no data in adolescents or premenopausal women)

Other Interventions for Bone

- **Denosumab** has not been studied in premenopausal women and animal studies suggest teratogenicity (*Bussiere JL et al., Repro Tox 2013*)
- **Metreleptin** can increase BMD and BMC in lumbar spine but numbers studied are too small to recommend Rx. Body fat mass was reduced (*Chou SH, et al, Proc Natl Acad Sci 2011*)
- In rare adult FHA cases, we suggest that short-term use of **rPTH** is an option in the setting of delayed fracture healing and very low BMD. Careful monitoring important.

Treatment of Patient with Hypothalamic Amenorrhea



Summary/Recommendations

3.7 We suggest *against* using bisphosphonates, denosumab, testosterone, and leptin to improve BMD in adolescents and women with FHA. (2|⊕⊕○○)

3.8 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|⊕○○○)

Case

29 year-old woman with 1 year of amenorrhea

- Noticed change in color of skin
- Studying ballet; dancing 3 times/week
 - Dances 6 hr/week
 - Losing weight...

Case (con't)

PMH:

- Age 14 – menarche
 - Regular periods
- Age 15 – lost 20 lb
 - 90 lb and 65 inches; BMI 15 kg/m²
- 2 years of amenorrhea
 - Regained to 115 lb with resolution (BMI 19.1 kg/m²)
- Past 5 years – vegan: low in protein
 - Breakfast: oatmeal, pumpkin seeds, almond milk
 - Lunch: vegetables, hummus
 - Dinner: salad chick peas, sweet potato, plantains

Case (con't)

ROS:

- No vomiting or laxative use
- Some constipation

Physical Examination:

- Height: 65 inches,
- Weight: 109 lb (BMI 18.1 kg/m²)
- Orange color to skin
- Pulse 58 BP 100/ 70
- Raynaud's (cool, mottled hands and feet)
- Pelvic normal
- Atrophic vaginal mucosa

Case (con't)

Laboratory Evaluation:

- β -HCG negative
- LH 1.1, FSH 3.4 μ U/mL – low normal
- Prolactin 5.8 ng/mL, E2 < 2 pg/mL (undetectable)
- TSH 0.85 μ U/L (0.5-4.3), Free T4 1.43 (0.82-1.77)
- Carotene 317 (6-77 mcg/dL)
- Chem profile with liver enzymes, CBC, AMH – WNL

- BMD Spine L1→L4 Z -3.0, Total hip Z -2.0

Case (con't)

- Norethindrone 5 mg for 10 days: no withdrawal bleeding
- Follow up:
- Nutrition - diet low in calories and protein
 - Fish and cheese added to diet
 - High carotene vegetables and fruits restricted
 - Weight gain advised
 - *Easier said than done in many cases...*
- Note history is vital in this case
- In six months, if no improvement in estradiol level, consider transdermal estradiol Rx
- Follow BMD; Carotene will decrease with change in diet

Case Question

Which Should be Considered in this Patient?

- A. Oral contraceptives should be added to bring on periods and improve mood
- B. Bone formation is suppressed and resorption is increased due to nutritional restriction
- C. If a patient has acne or hirsutism she cannot have HA
- D. BMD will only improve with E2 therapy

Case Answer

Which Should be Considered in this Patient?

- A. Oral contraceptives should be added to bring on periods and improve mood
- B. Bone formation is suppressed and resorption is increased due to nutritional restriction
- C. If a patient has acne or hirsutism she cannot have HA
- D. BMD will only improve with E2 therapy

II. Scope of the Problem

Fertility Options for Women with Functional Hypothalamic Amenorrhea

Treatment Goals for Women with FHA

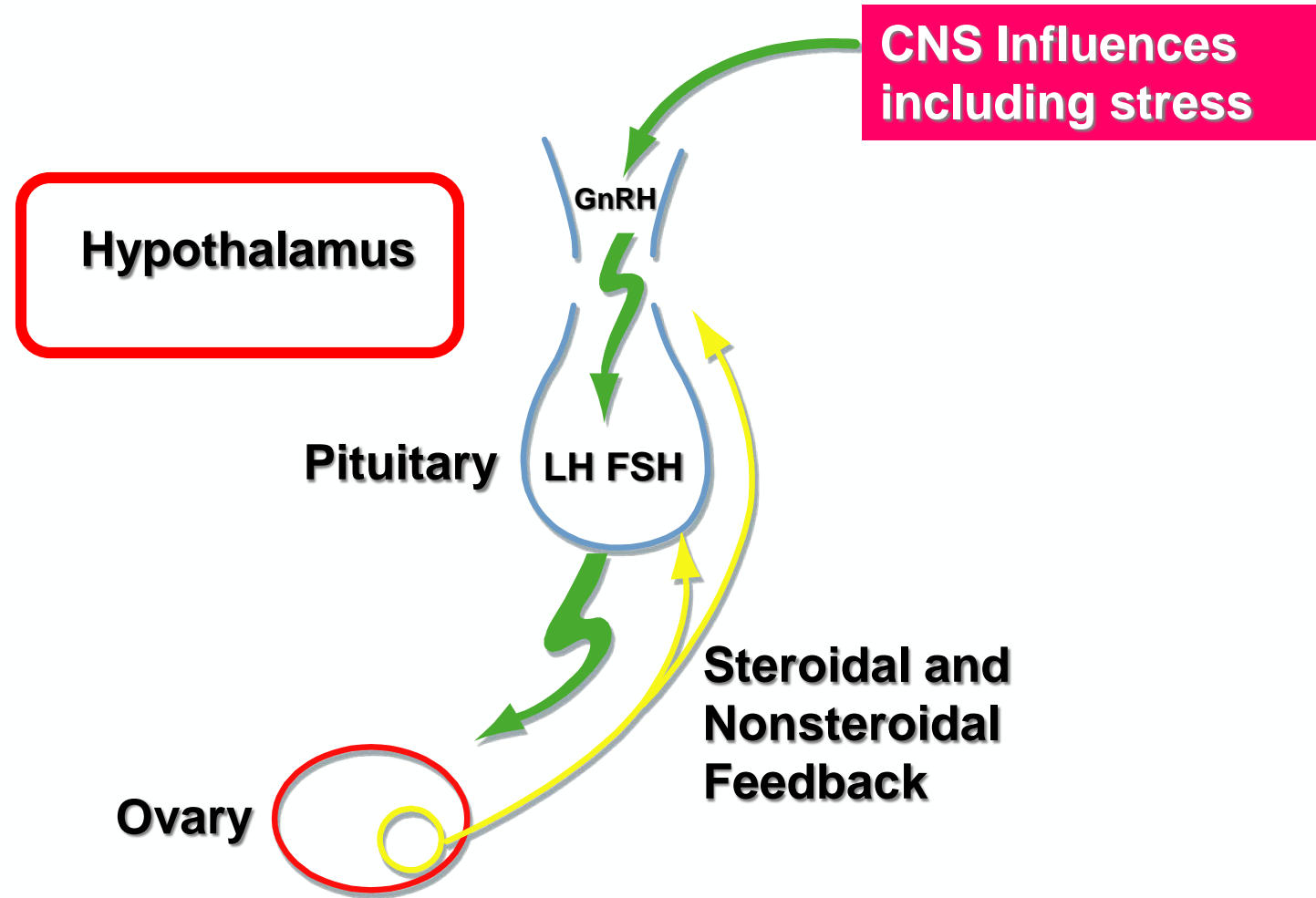
- Ovulation induction
- Fertilization
- Implantation
- Singleton pregnancy
- Genetically normal fetus
- Appropriate fetal growth and development
- Term gestation

Which are safest for Mom? Baby?

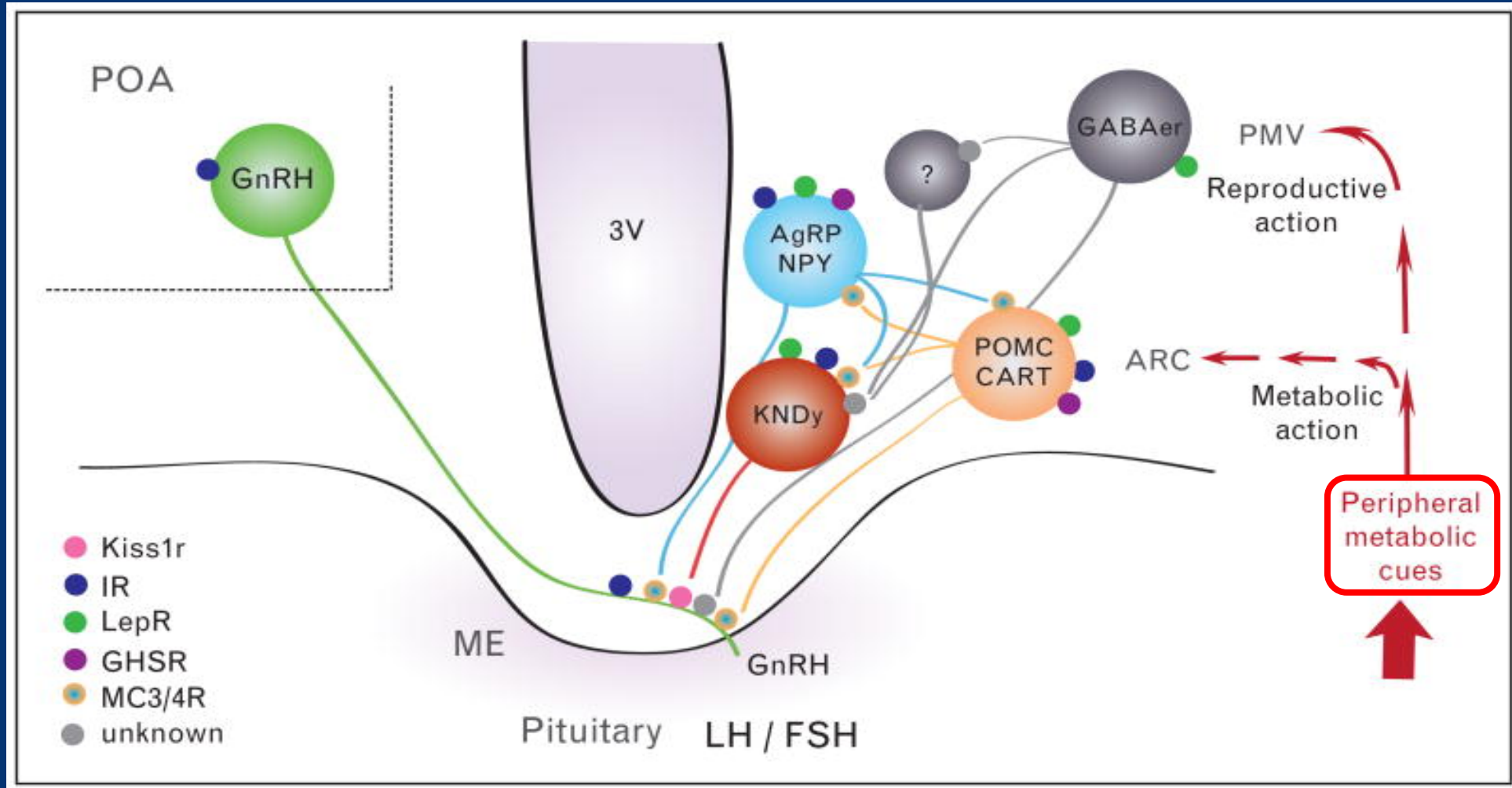
Treatment Options

- SERMS such as clomiphene citrate
- Aromatase inhibitors such as letrozole
- Exogenous gonadotropins \pm IVF
- Pulsatile GnRH
- Kisspeptin
- Leptin
- Psychotropics
- Behavioral therapies such as cognitive behavior therapy (CBT)

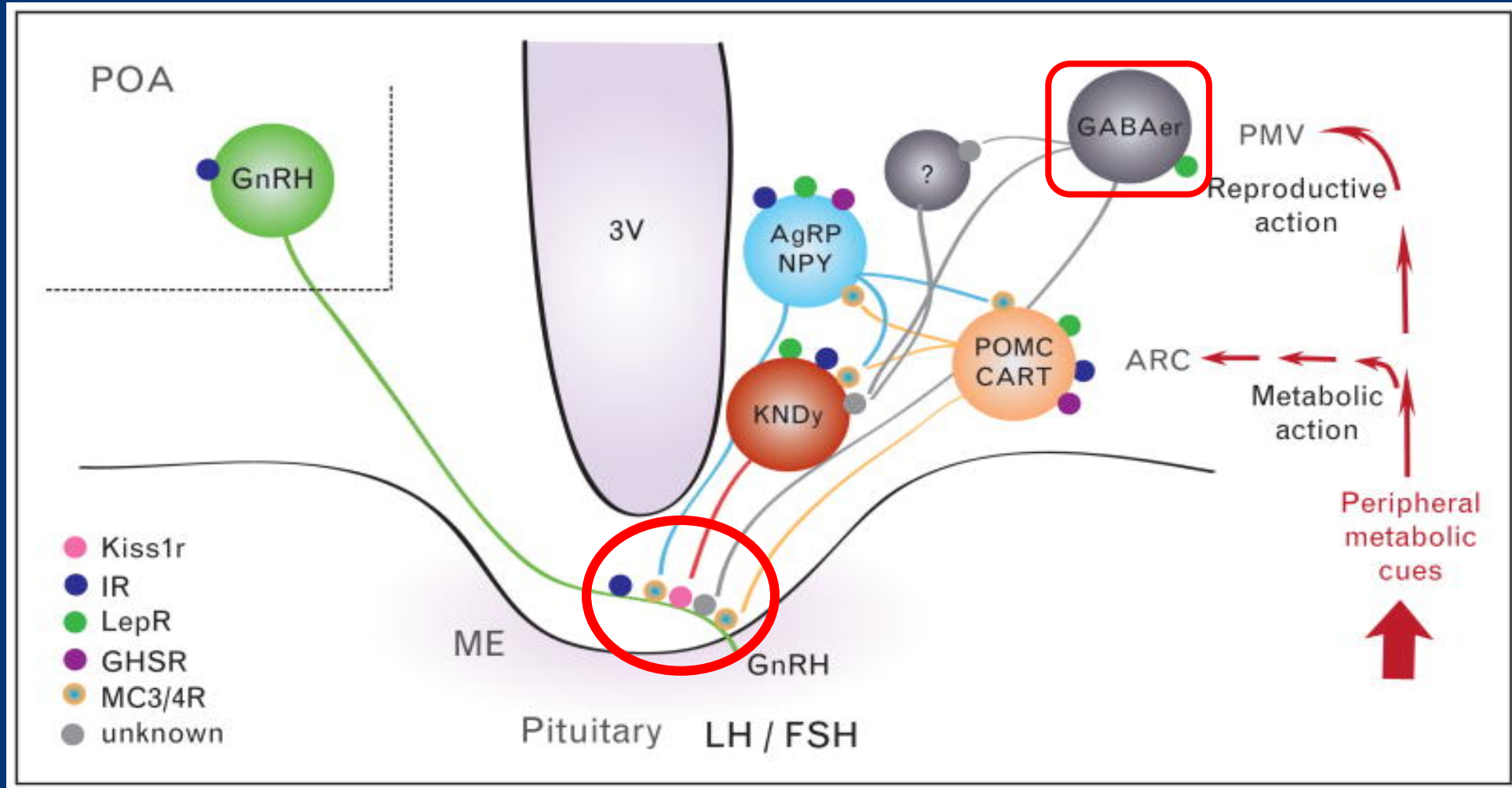
FHA: More than Isolated Disruption of GnRH Drive...



Metabolic Influences on Neuroendocrine Regulation of Reproduction



Metabolic Influences on Neuroendocrine Regulation of Reproduction



Treatment Limitations

- SERMS such as clomiphene citrate
- Aromatase inhibitors such as letrozole
 - May not work due to increased feedback sensitivity of GnRH to estradiol
 - Unlikely to correct other endocrine concomitants
 - May impair endometrium and reduce likelihood of implantation

Treatment Limitations (cont.)

- Exogenous gonadotropins \pm in vitro fertilization
 - Expensive
 - Injectables are cumbersome to administer
 - Requires frequent monitoring with ultrasound and estradiol levels
 - High risk of ovarian hyperstimulation
 - High risk of multiple gestation without IVF and elective single embryo transfer
 - Unlikely to correct other endocrine concomitants

Treatment Limitations (cont.)

- Pulsatile GnRH
- Kisspeptin
- Leptin
 - Limited or nonexistent commercial availability
 - Unlikely to correct other endocrine concomitants
 - Protein hormones are difficult to manufacture and administer
 - If available, likely to be expensive

Treatment Limitations (cont.)

- Psychotropics
 - May reduce stress and restore appetite
 - No clinical trials of impact on fertility and reproductive outcomes
 - May ameliorate other endocrine concomitants
 - Fetal exposure if not promptly discontinued

Treatment Limitations (cont.)

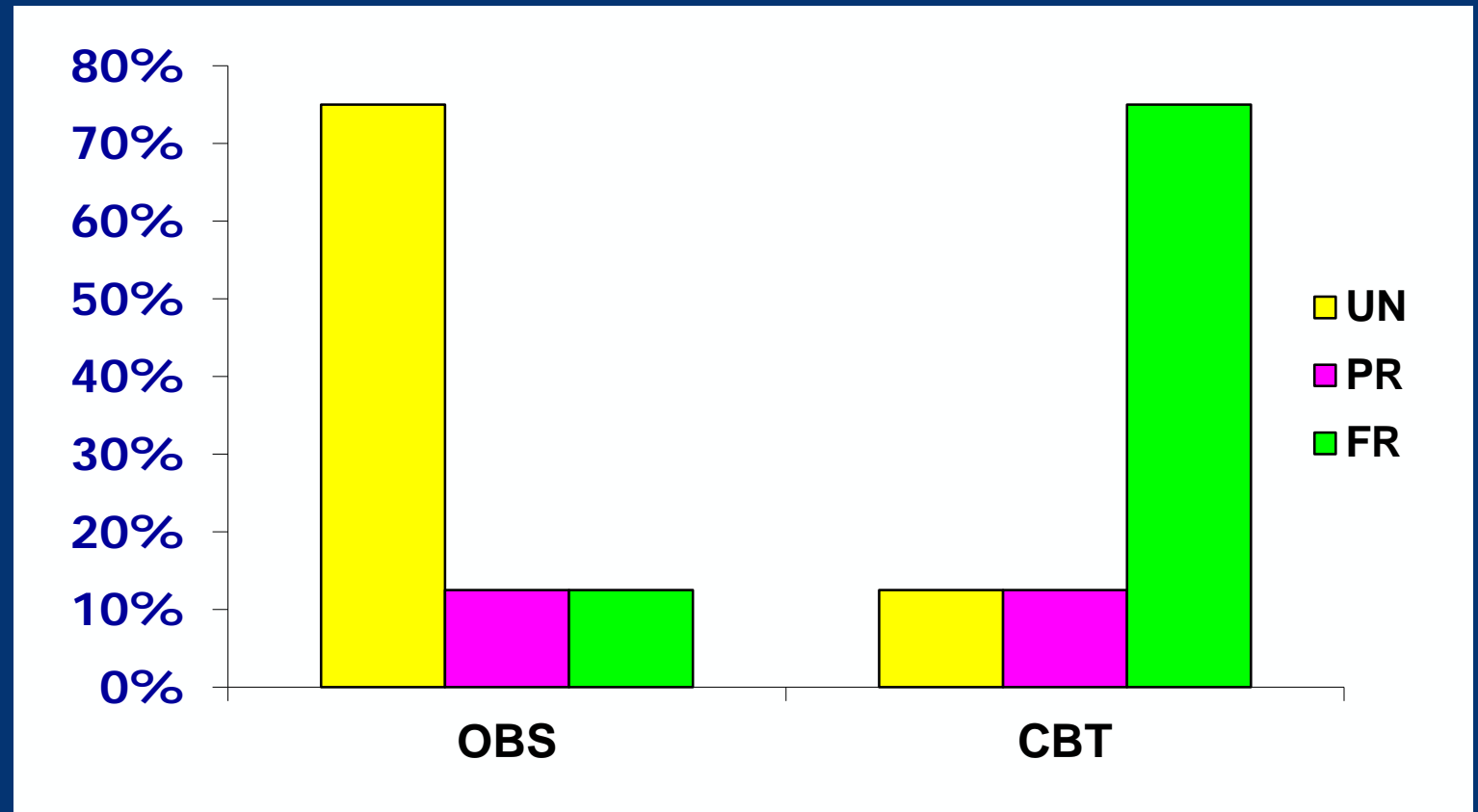
- Behavioral therapies such as cognitive behavior therapy (CBT)
 - CBT shown to effectively restore ovulation in those with normal BMI in only pilot study
 - CBT ameliorated other endocrine concomitants
 - Inexpensive
 - Limited availability of trained personnel
 - Benefit accrues indefinitely

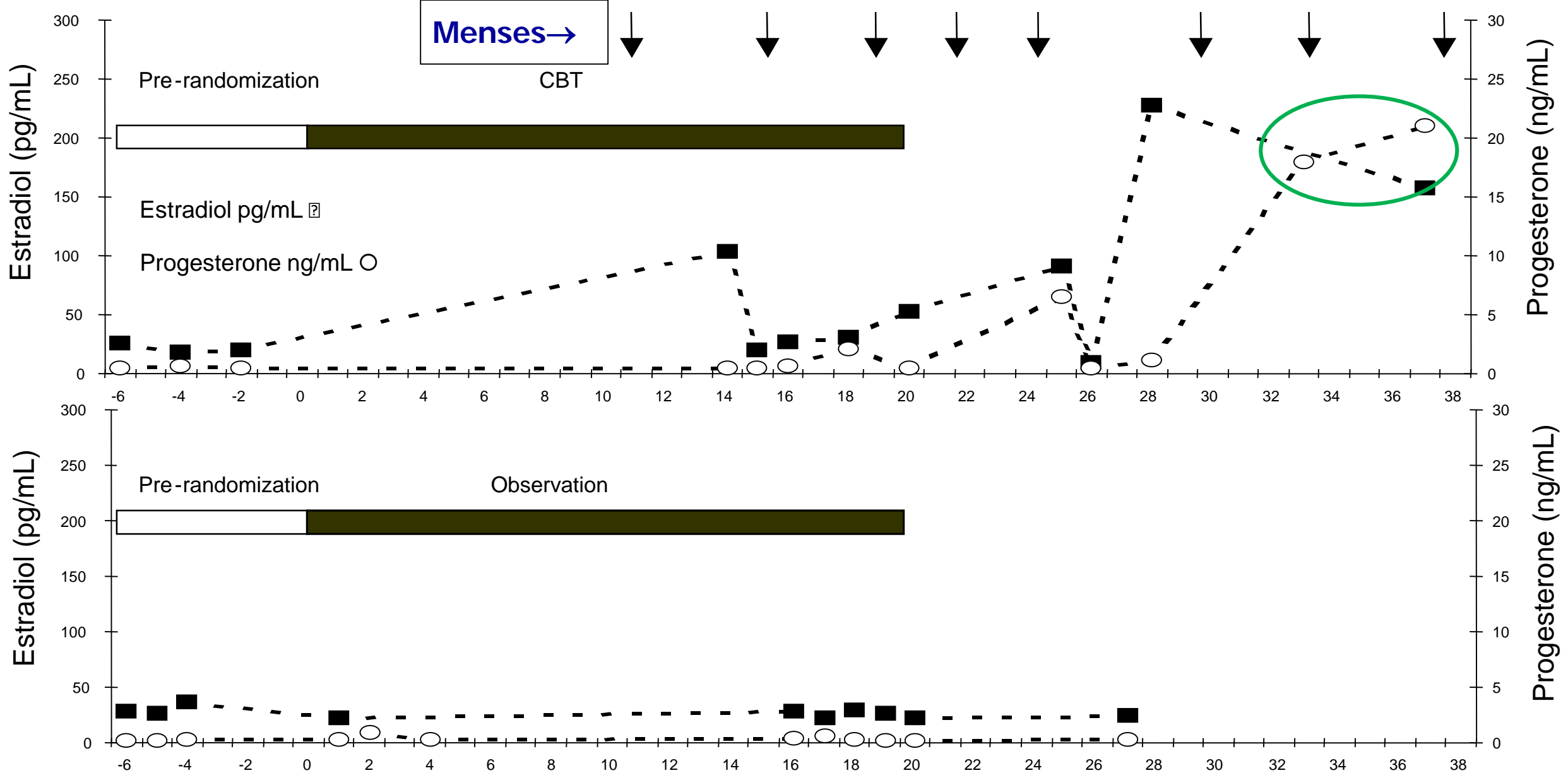
Cognitive Behavior Therapy for Stress-Induced Anovulation (FHA)

Aim of CBT was to change attitudes and restore internal locus of control rather than prescribe behavior change

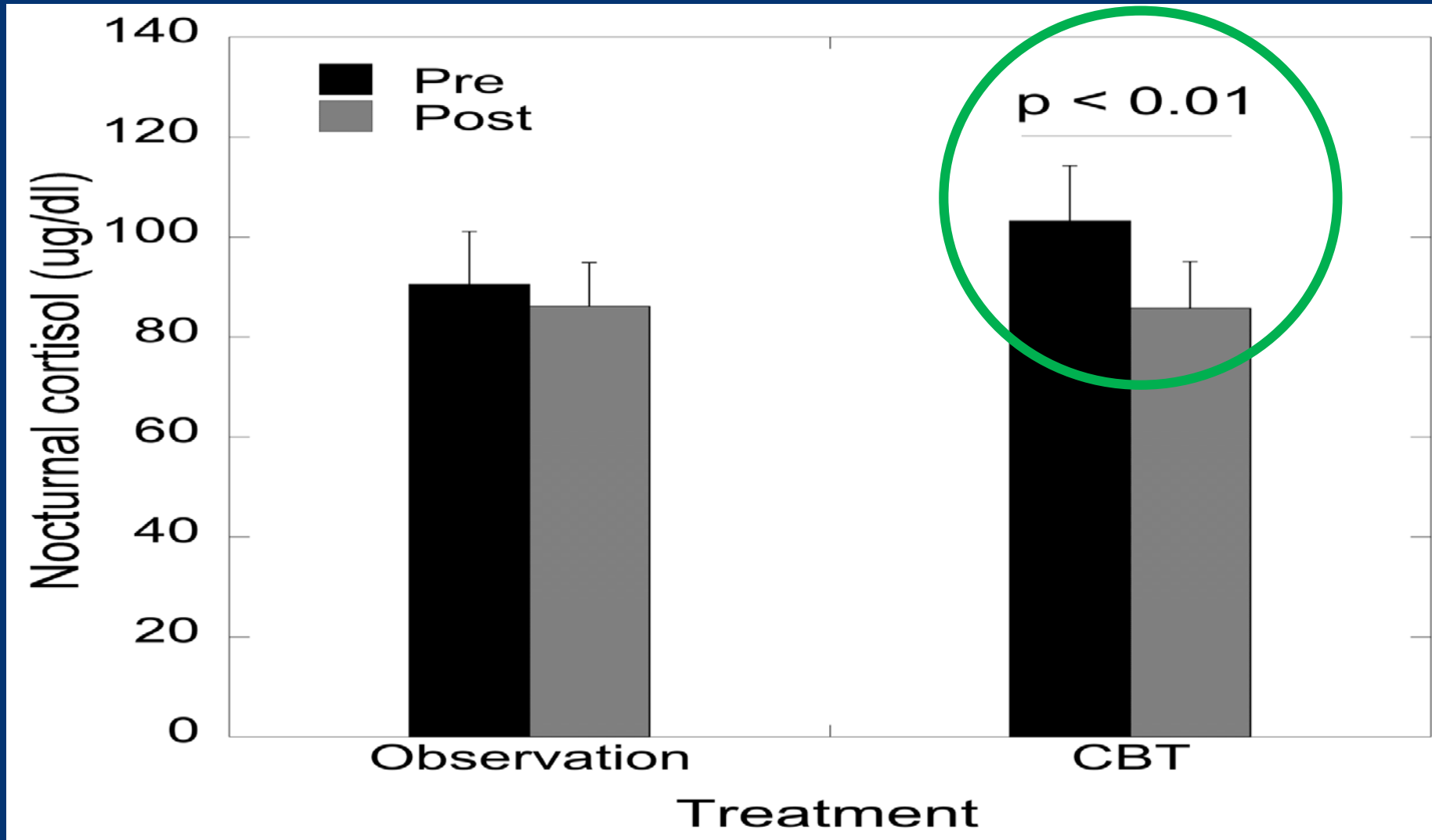
16 sessions, 45 min each, over 20 weeks

Ovarian responses to observation vs CBT in FHA

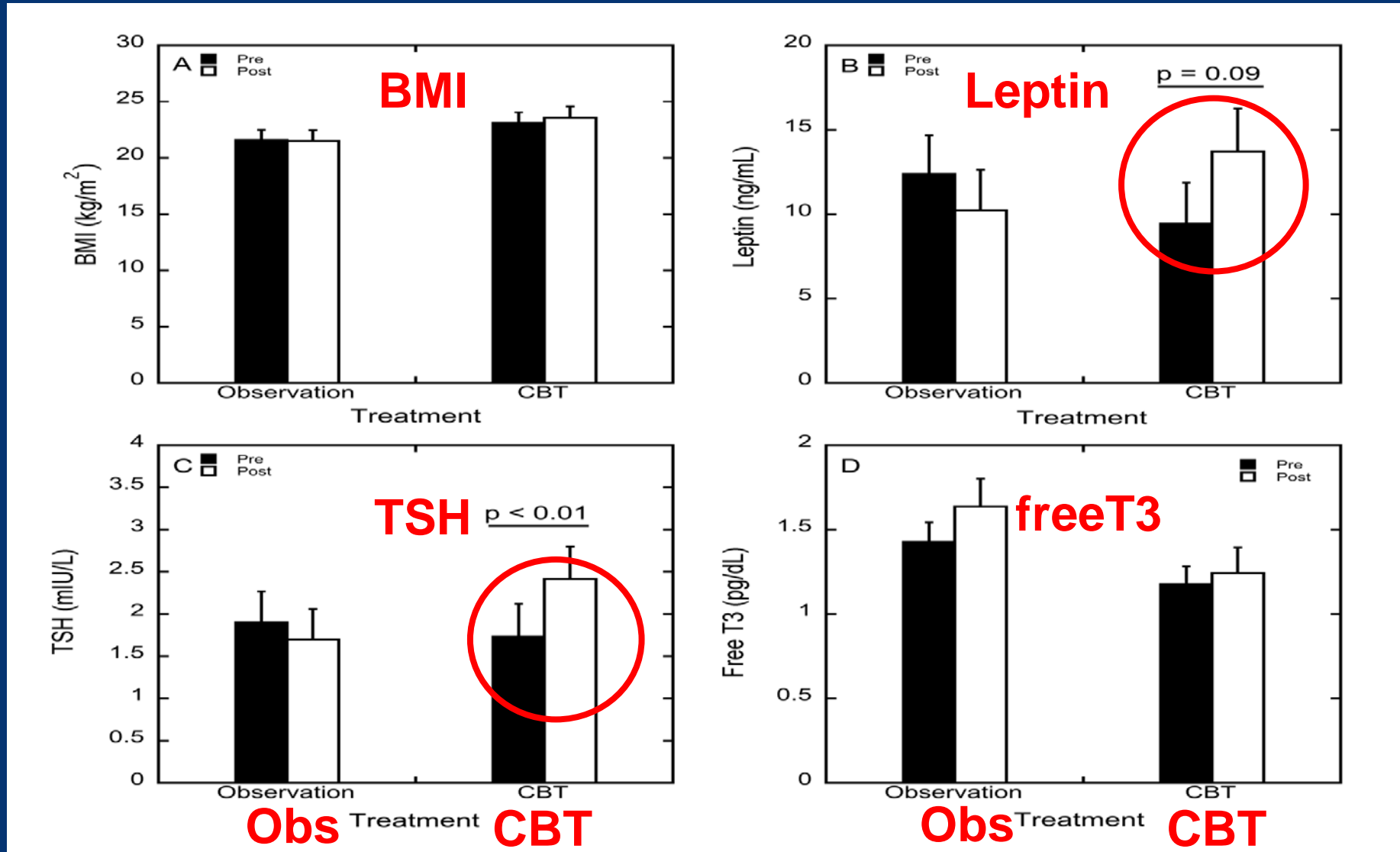




CBT Reduced Circulating Cortisol In FHA



Leptin and TSH increased following CBT



Treatment Options For FHA

- Ovulation induction / in vitro fertilization
 - SERMs / AIs / Gonadotropins / GnRH
- Behavioral interventions and psychotropics
- Both
- All approaches have pros and cons, but behavioral interventions cost the least, safeguard maternal and fetal health, and have enduring impact

Treatment of FHA and Concomitant Medical Conditions

3.9 In patients with FHA wishing to conceive, after a complete fertility work-up, we suggest:

- Treatment with pulsatile gonadotropin-releasing hormone (GnRH) as a first line, followed by gonadotropin therapy and induction of ovulation when GnRH is not available (2|⊕○○○);
- Cautious use of gonadotropin therapy (2|⊕○○○);
- A trial of treatment with clomiphene citrate for ovulation induction if a woman has a sufficient endogenous estrogen level (2|⊕○○○);
- Against the use of kisspeptin and leptin for treating infertility (2|⊕○○○); and
- 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|⊕⊕○○)

Treatment of FHA and Concomitant Medical Conditions

3.10 We suggest that clinicians should only induce ovulation in women with FHA that have a **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|⊕⊕○○)

Evaluation

2.9 In patients with FHA and underlying PCOS, we suggest:

- Clinical monitoring for hyper-response in those treated with exogenous gonadotropins for infertility.
(2|⊕⊕○○)

III. Content Review and Summary

Answer to Case Study

Many Common Themes...

- That span the age spectrum
- Unique issues to consider in cases of FHA manifesting as primary amenorrhea
 - Adolescents with open epiphyses
 - Height potential and concerns
- Adult women with FHA
 - Monitoring of BMD
 - Close attention to 'energy balance'
- Women wishing to conceive
 - Present with unique set of issues

Correct the Energy Deficit...

3.2 In adolescents and women with FHA, we recommend correcting the energy imbalance to improve HPO axis function; this often requires behavioral change. Options for improving energy balance include increased caloric consumption, and/or improved nutrition, and/or decreased physical activity. This often requires weight gain. (1|⊕⊕⊕○)

3.3 In adolescents and women with FHA, we suggest psychological support, such as CBT. (2|⊕⊕○○)

- Assess for in cases of FHA – adolescents or women
- Address, if found

Adult/Adolescent With FHA

- We suggest that clinicians obtain a baseline BMD measurement by dual-energy X-ray absorptiometry (DXA) from any **adolescent or woman** with 6 or more months of amenorrhea, and that clinicians obtain it earlier in those patients with a history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility. (2|⊕⊕⊕○)
- *Close monitoring of bone health needed in patients with FHA across the age spectrum*

Case

14 year-old with primary amenorrhea

- Pubic hair development at age 11 years
- Breast development at age 12 years
 - Tanner III breasts (+ pubic hair), notes from PCP
- “Grew a lot” (height spurt) 2 years ago
- Never started menses
- Otherwise healthy
- Elite dancer with local dance company
 - Straight A student
 - Attends high school affiliated with company
- Denies eating disorder

Case (cont.)

Physical Examination

- Weight – 5th %ile; Height 10%ile; BMI 19.5 kg/m²
- Vital signs: HR - 58 BP - 104/70
- Tanner III breasts and pubic hair
- Notable for: Thin, no hirsutism or acne, normal external genitalia, but vaginal mucosa – red/atrophic

Laboratory work-up

- Urine pregnancy (*not sexually active, but....*)
- Free T4 + TSH - low normal
- FSH + LH - low normal, FSH predominance

Case (cont.)

Evaluation

- Estradiol -10 pg/mL (low)
- AMH - normal
- Prolactin - normal
- CBC – normal
- Sedimentation rate - normal
- Chem-7 panel - normal
- Liver function tests - normal

Case Question

What would you do next?

- A. Full bimanual/pelvic examination
- B. Pelvic MRI
- C. Pelvic ultrasound: abdominal +/- transvaginal
- D. Morning 17-hydroxyprogesterone

Case Answer

What would you do next?

- A. Full bimanual/pelvic examination
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Case

14 yo with primary amenorrhea

What would you do next?

- A. Full bimanual/pelvic examination
- B. Pelvic MRI
- C. **Pelvic ultrasound**: abdominal +/- transvaginal
- D. Morning 17-hydroxyprogesterone

2.2 In a patient with suspected FHA, we recommend excluding pregnancy and performing a full physical examination, including a gynecological examination (external, and in select cases, bimanual), to evaluate the possibility of organic etiologies of amenorrhea. (1|⊕⊕⊕○)

In most young, non-sexually active teens, a pelvic ultrasound would be appropriate

- External exam – YES
- Bimanual exam - NO