Anorexia Nervosa and Estrogen: One hardworking hormone!

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Debra K. Katzman, MD, FRCPC
Professor of Paediatrics
Senior Associate Scientist Research Institute
Hospital for Sick Children and University of Toronto

Mark Norris, MD, FRCPC
Associate Professor of Paediatrics
Children’s Hospital of Eastern Ontario

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  - CHEO RI (MN)
  - Farm Boy (MN)
  - Bell Let's Talk (MN)
  - Mach Gaensslen (MN)

- Other
  - LWW (DK)
Objectives

• At the completion of this presentation, you will:
  • Understand the important roles of estrogen in adolescents with anorexia nervosa (AN).
  • Recognize that the associations of estrogen/AN change across the spectrum of illness and have implications for both etiological models and treatment
  • Explore the role of estrogen preparations as an effective treatment for bone, mood and cognition in adolescents with AN

Case: Julia

• 17.5 year old female with 3-year history of AN
• Premorbid weight = 51 kg at 14 years (50th percentile)
• Current weight = 35.7 kg (<3rd percentile; 60% of expected)
• Followed as outpatient - 5 hospital admissions for severe weight loss
• Unable to gain or sustain weight gain
• History of depressed mood and increased social anxiety
• Menarche at age 12, LNMP at age 14.7 years
• BA (x-ray of L wrist) = 16 years
• No fracture history
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Anorexia Nervosa

- AN characterized by
  - Eating restriction
  - Repeated and obsessive fears of being fat
  - Voluntary pursuit of thinness (Bulik et al, 2005)
Anorexia Nervosa: DSM-5 Criteria

- Restricting type
  - weight loss is accomplished primarily through dieting, fasting and/or excessive exercise.

- Binge-eating/purging type
  - recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Anorexia Nervosa

- Prevalence of 0.3-0.6% (Hoek, 2006; Hudson et al, 2007)
- Peak age of onset 15-19 years old (Favaro et al, 2009)
- AN more common in women/girls than men/boys
  - F:M ratio = 10:1 older adolescents and adults
  - F:M ratio = 6:1 children < 12 years (Pinhas, 2011)
Anorexia Nervosa

• Medical and psychiatric co morbid conditions are associated with AN

• Highest mortality rate of any psychiatric disorder (Millar et al, 2005)
  • 5.86 deaths in 1000 AN patients per year (Arcelus et al., 2011)
  • Malnutrition and suicide

Anorexia Nervosa

• Etiology unknown making treatment difficult
• Treatment is complex and includes
  • Weight restoration
  • Correction in disturbances of body image
  • Treatment of acute and chronic medical complications
  • Treatment of comorbid psychiatric disorders
Anorexia Nervosa

- Psychotherapies
  - Family-based therapy, first-line (Lock and le Grange)
  - Significant patterns of benefit across time
  - Treatment response is good

- Pharmacological treatment
  - Limited in terms of clinical benefits

Anorexia Nervosa

- Drug therapies more focused on medical complications
  - Bone
  - Cognition
  - Mood
  - ESTROGEN
Effects of estrogen on bone, mood and cognition in anorexia nervosa

The premise

- Estrogen plays a role in AN
  - Estrogen's role in AN is complicated
  - Changes in estrogen levels play different roles in AN
    - *Increased levels of* estrogen may confer risk for development of AN
    - *Decreased levels* of circulating estrogen perpetuate AN in young women
    - *Estrogen replacement rx* may be important for the treatment of some aspects of AN
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Estrogen may confer risk for AN

- The estrogenic pathway in women with AN is supported by
  - AN more common in women/girls than men/boys (Hudson *et al*, 2007; Ramoz *et al*, 2007).
  - The onset of AN around puberty is correlated to the presence of estrogenic peaks.
  - The anorexic effect of high estrogen levels was found in animal models (Couse and Korach, 1999; Wade and Gray, 1979).
  - Turner's patient treated with estrogen develop symptoms of AN after starting estrogen.
  - Women have decreased caloric intake during menstrual cycle when levels of estrogen are elevated (Asarian and Geary, 2006).
Menstrual cycle of healthy adolescents
Estrogen may confer risk for AN

- Family studies
  - Higher frequency of AN in relatives of patients compared to relatives of controls — heritability of 70% (Hinney et al., 2010)
  - Concordance between monozygotic twin and dizygotic twins heritability of 90% (Bulik et al. 1998; Gorwood et al. 2003; Hinney et al. 2010)
  - Twin studies support puberty (rises in estrogen) as a period of significant genetic risk for eating disorders (Culbert et al. 2008; Procopio and Harris, 2007)
  - Minnesota Twin Family Study shows that there was negligible genetic effects on eating pathology before puberty, but onset of puberty had increased genetic effect on onset of AN (Klump et al., 2007a)

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Hypogonadotropic Hypogonadism in AN

Low energy availability
↓ Gonadotropin secretion

Estrogen levels in adolescents with AN (Misra, 2008)
LH levels throughout puberty

Boyar et al., NEJM, 1974

LH Secretory Pattern in AN

Boyar et al., NEJM, 1974
Estrogen effects on serotonin

- Estrogen’s effects on serotonin
  - Increases the sensitivity of the receptors that receive serotonin
  - Increases the number of serotonin receptors which increases the activity level of serotonin
  - Increases the reuptake of serotonin
  - Increases the synthesis of serotonin

Serotonin (5-HT) and AN
The premise

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Effects of estrogen on bone, mood and cognition in anorexia nervosa
Anorexia nervosa, bones and estrogen

- Well established that anorexia nervosa (AN) has a negative impact on bone health in adolescent girls.
- AN is associated with profound malnutrition and amenorrhea
- Chronic consequences of malnutrition and amenorrhea
- Poor bone health

Adolescence is a critical time for bone mass accrual

\[ \triangle \text{L2-L4 BMC} \]

\[ \text{Age} \]

Theintz, 1992
Background: Adolescence and AN

Peak bone mass

Age

Bone mineral content

Mechanisms Contributing to Low Bone Density in AN

Low weight and lean body mass
GH resistance and low IGF-I
High cortisol
Alterations in other hormones
  High PYY and ghrelin
  Low leptin
Calcium and vitamin D
Low estrogen

Decrease Formation and Resorption
Adolescent-onset AN and BMD

• The facts
  • > 90% of adolescents and young adults with AN have reduced BMD at one or more skeletal sites (Grinspoon, 2000)
  • The rate of bone loss during active disease is ~ 2.5%/year (Miller, 2006)
  • Adolescents with AN do not increase their bone mass (Sokya, 2002; Misra et al, 2008)
  • Adults with adolescent-onset AN have lower LBMD than those with adult-onset AN, despite comparable years of amenorrhea (Biller, 1989)
  • Low BMD acquired during adolescence may impose life-long increased fracture risk (Lucas, 1999; Johnell, 2005)

Decreased Bone Mineral Accrual in AN

Soyka, 2002
Adolescent-onset AN and BMD

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Therapeutic Strategies

• Weight gain and menses resumption
  • Optimal strategy for improving bone accrual in AN
  • Residual deficits persist (Misra, 2008; Basrurach 1991; Katzman 1991)

• Bisphosphonates
  • Modest increase in femoral BMD (Golden, 2005)

• Estrogen replacement (Sims, 2010)
  • Estrogen preparations - all oral
  • 4 RCTs and 2 cohort studies that include adolescents and young women
  • 1 RCT and 2 cohort study each in adolescents
## Therapeutic Strategies with Oral EPs

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study Design</th>
<th>Description of Patients with AN</th>
<th>Interventions</th>
<th>Type of Control</th>
<th>Assessment and Location of Bone Mass</th>
<th>Duration of Follow-Up (Mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golden (2002)</td>
<td>Cohort</td>
<td>50 adolescent and young adult (13-21 years)</td>
<td>25-35 µg</td>
<td>No medication</td>
<td>Lumbar spine, femoral neck DXA</td>
<td>12</td>
</tr>
<tr>
<td>Gordon (2002)</td>
<td>RCT</td>
<td>61 (14-28 years)</td>
<td>20 µg EE/0.1mg levonorgestrel</td>
<td>DHEA</td>
<td>Lumbar spine, femoral neck and total body DXA</td>
<td>12</td>
</tr>
<tr>
<td>Grinspoon (2002)</td>
<td>RCT</td>
<td>61 (14-28 years)</td>
<td>35µg EE/0.4mg norethindrone</td>
<td>Placebo</td>
<td>Lumbar spine, femoral neck, radius, and total body DXA</td>
<td>9</td>
</tr>
<tr>
<td>Klibanski (1995)</td>
<td>RCT</td>
<td>48 (16.3-42.5 years)</td>
<td>0.625 mg Premarin/5 mg Provera</td>
<td>No medication</td>
<td>Spinal CT</td>
<td>18</td>
</tr>
<tr>
<td>Munoz-Calvo (2007)</td>
<td>Cohort</td>
<td>20 (mean age –17.3 years)</td>
<td>35µg EE</td>
<td>No medication</td>
<td>Lumbar spine DXA</td>
<td>12</td>
</tr>
<tr>
<td>Strokosch (2006)</td>
<td>RCT</td>
<td>146 adolescents (11-17 years)</td>
<td>35 µg EE</td>
<td>Placebo</td>
<td>Lumbar spine, femoral neck DXA</td>
<td>13</td>
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## Differential effects of oral vs. transdermal administration

- **Oral estrogen**
  - First pass effect through liver
  - Decreases IGF-1 (bone trophic) levels by suppressing mRNA of IGF-1 in liver
  - Suppression of systemic IGF-1 in post-menopausal women (Weissberger, 1991)

- **Transdermal estrogen**
  - Avoids the hepatic first-pass effect and does not have an impact on IGF-1 levels
  - Provides constant serum levels similar to ovarian estradiol secretion
  - Used in Turner syndrome and resulted increases in BMD (Naha, 2009)
  - Have not been studied in AN
Methods

Girls with AN
12-18 yrs
MGH and SickKids
N=110

Girls with AN
BA <15 yrs
N=14

Girls with AN
BA ≥15 yrs
N=96

Placebo

Placebo

3.75 mcg ethinyl estradiol daily from 0-6 months
7.5 mcg EE daily from 7-12 months
11.25 mcg EE daily from 13-18 months

100 mcg transdermal estrogen
* 2.5 mg medroxyprogesterone acetate pills for days 1-10 of each month

Baseline DXA Measures

![Graphs showing BMD (g/cm²) for spine and hip, BMD Z-scores for spine and hip, and weight (kg) for fat and lean mass.](image)
Results

• Intent to treat repeated measures analysis

• Spine and hip BMD Z-scores increased significantly in girls with AN who received estrogen versus placebo (p<0.05)
  • For the group as a whole
  • Similar results in a post hoc analysis of mature girls alone (n=96)

• IGF-I levels did not change

% Change in Lumbar BMD
% Change in Hip BMD

Summary

- Physiologic estrogen replacement is an effective strategy to increase bone accrual in adolescents with AN.
- Bone accrual rates do need exceed that found in controls - accrual is about the same.
- No catch-up in BMD.
- Estrogen found to be a potentially important treatment.
Anorexia nervosa, mood and estrogen

- Low levels of circulating estrogen may adversely impact mood
  - Ovariectomized, hypogonadal rats treated with estrogen perform better than controls during a forced swim test by swimming more and struggling less (Rachman et al, 1998; Diz-Chaves et al 2012)
  - Ovariectomized, hypogonadal rats treated with estrogen tend to be less immobile and display less anxiety-like behavior on the mirror maze test
  - Adolescents and adults with Turner Syndrome or premature ovarian failure have higher anxiety levels (Lasalite L, et al 2010; Cardoso et al 2004; Schmidt Pj et al 2006)

Effect of Transdermal Estrogen on Anxiety, Body Shape Perception and Eating Attitudes

- Anxiety
  - Spielberger's State-Trait Anxiety Inventory for Children (STAIC)
- Eating attitudes and behavior
  - Eating Disorders Inventory II (EDI II)
- Body shape perception
  - Body Shape Questionnaire (BSQ-34)
- Mature AN girls who completed questionnaires at baseline
  - Baseline: 72
    - 38 E+ 34 E-
  - 18 months follow-up: 37
    - 20 E+ 17 E-
- Completers vs. non-completers: no difference for baseline characteristics, use of psychotropic drugs, weight changes over time
Changes in EDI II subscale scores and BSQ-34 scores

Changes in STAIC trait and state
Anorexia nervosa, mood and estrogen

- Estrogen replacement improved trait anxiety (the tendency to be prone to anxiety) independent of weight changes
- Estrogen did no have an impact eating attitudes or body shape perception

Girls in placebo group (estrogen deficient state) who had increases in weight or BMI showed increases in eating disorder psychopathology and state anxiety

Girls receiving transdermal estrogen (estrogen replete state) who experienced increases in weight or BMI did not experience increases in psychopathology or state anxiety

Better chances at sustaining weight recovery in an estrogen replete vs estrogen deficient state
Anorexia nervosa, cognition and estrogen

• Low levels of circulating estrogen may adversely impact on cognition
  • Postmenopausal women (Yaffe et al., 1999; Miller et al., 2002)
  • Surgically menopausal women (Nappi et al., 2002)
  • Premature ovarian failure (Ross et al., 2004)
  • Turner syndrome (Ross et al., 2004)
  • Healthy menstrual cycle (Maki et al., 2002)

Subject Characteristics

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<th>Females with AN history (n=67)</th>
<th>Female controls (n=42)</th>
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<tr>
<td>Age at study, yr</td>
<td>21.3 ± 2.3</td>
<td>20.7 ± 2.5</td>
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<td>Education, yr</td>
<td>14.5 ± 2.0</td>
<td>14.3 ± 2.3</td>
</tr>
<tr>
<td>Hollingshead SES</td>
<td>50.1 ± 10.4</td>
<td>48.5 ± 11.2</td>
</tr>
<tr>
<td>Age of onset, yr</td>
<td>13.3 ± 1.5</td>
<td>-</td>
</tr>
<tr>
<td>Lowest BMI, kg/m²</td>
<td>15.3 ± 1.7</td>
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<tr>
<td>Follow-up duration, yr</td>
<td>6.4 ± 1.7</td>
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<tr>
<td>BMI at study, kg/m²</td>
<td>21.8 ± 3.4*</td>
<td>24.3 ± 4.3</td>
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*p=0.001
Menstrual function

67 females with AN history

18 amenorrhea or irregular menses

49 regular menses or oral contraceptive pill

42 controls

* As reported for the past 6 months prior to study

WJ-III by menstrual function

* p<.05, ** p<.01, vs control; ∆p<.05 vs irregular
Verbal & visual memory by menstrual function

- Irregular or absent menses (n=18)
- Pill or regular menses (n=49)
- Control (n=42)

**log scores (+SD)**

* p<.05 vs control

1.5
1
0.5
1
2
2.5

- Total Recall
- Delayed recall
- Recognition Discrimination Index
- Visual reproduction
- Visual reproduction - delayed

Anorexia nervosa, cognition and estrogen

- Failure to resume normal menstrual function is associated with persisting cognitive impairments.
- Oral estrogen/menstrual recovery (normal levels or estrogen) is an important correlate with cognitive functioning in AN.
So, how do we understand all of this...

- Results suggest an association between estrogen and AN
- There appears to be the presence of differential hormone effects
  - Onset of the disorder - precipitated by higher levels of estrogen
  - Maintenance of the disorder - lower levels of estrogen
  - Studies showing the positive impact of physiologic estrogen on certain medical complications
  - This has implications for both understanding the disorder and for treating the disorder

Another ED paradigm: Bulimia nervosa

(Klump et al, submitted)

- Studies have looked at adult women with BN
- Strong associations between binge eating and ovarian hormones
- Low risk of binge eating
  - High estrogen and Low progesterone
- High risk of binge eating
  - High on both
  - Low on both
Moving forward…

- We can no longer think of AN/eating disorder as uni-dimensional
- These are complicated disorders
- Hormones play a variety of roles
- Role of other hormones /progesterone/complex interactions
- Helpful to go outside of eating disorders and look at other illnesses to develop novel approaches – mood disorders

Take Home Points

- Changes in estrogen levels play a role in AN
- Responses to increased levels of estrogen contribute to risk for the development of AN
- Responses to low levels of estrogen contribute to maintenance of AN
- Actions of estrogen replacement positively impact bone, mood and cognition in young women with AN
Case: Julia

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Questions to consider

- Among other treatment options, is there any role for estrogen replacement in this patient?
- When should estrogen, if used, be implemented? Why?
- What are the challenges in using estrogen (oral, transdermal)?
- What if an adolescent female with AN was sexually active? What kind of contraception would you recommend?
- What about patient's mood/social anxiety?
- What are the next steps?