A randomized trial of hormonal add-back therapy for adolescents treated with gonadotropin releasing hormone agonist for endometriosis

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I have no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

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Background

- Endometriosis is a debilitating disease complicated by pain, limitation of activities, and poor social function
- Gonadotropin releasing hormone agonists (GnRHa) are utilized for patients who have failed primary therapy
- Long-term GnRHa use is associated with deleterious effects on bone mineralization; adults lose 5-8% BMD in 3-6 mos of tx
Research Questions

- Add-back therapy is a promising adjunct to treatment, but never studied in adolescents
- Adolescents are at highest risk for the negative impact of GnRHa
- Was GnRHa plus add-back therapy with norethindrone acetate (NA) + conjugated equine estrogens (CEE) or NA + placebo superior to maintain bone health in adolescents treated with GnRHa for endometriosis

Methods

- Adolescents (n=51) initiating GnRHa therapy for endometriosis prospectively recruited at BCH from 2003-2008
- Randomized, double-blind, placebo-controlled trial
- Assignment to add-back therapy with either:
  - NA 5 mg PO daily + CEE 0.625 mg PO daily
  - NA 5 mg PO daily + placebo PO daily
- Treatment administered for 12 mos
- Study approved by the BCH IRB

Sample Recruitment

Inclusion criteria
- Age 15-22 y
- ≥ 2 y post-menarche
- Surgical diagnosis of endometriosis
- GnRHa therapy

Exclusion criteria
- Other diseases (celiac, DM) or medications (steroids) known to affect BMD
Methods: Outcome Measures

- Areal bone mineral density (BMD), bone mineral content (BMC), and body composition measures were obtained by DXA at baseline, 6 mos, and 12 mos
- Anthropometrics, quality of life measures, and laboratory studies were collected at 0, 3, 6, and 12 mos
  - Safety measures: LFTs, lipid panels

Methods: Statistical Analyses

- Baseline comparison of continuous measures between trial arms: Student t-test, Wilcoxon two-sample test, Fisher exact test
- Analysis followed the intention-to-treat principle
  - Repeated measures ANOVA
  - Primary test of treatment efficacy was time × treatment interaction
  - Variables with highly skewed distributions were log-transformed for analysis and retransformed for reporting
- Trial designed with 80% power to detect a rate of change of 0.017 g/cm²/yr in hip BMD

Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Participants (n=51)</th>
<th>NA + CEE Arm (n=25)</th>
<th>NA + P Arm (n=26)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min—Max</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>17.9 ± 1.7</td>
<td>15.4—22.6</td>
<td>17.7 ± 1.4</td>
<td>0.41</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.8 ± 4.8</td>
<td>155.6—176.6</td>
<td>162.9 ± 4.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.8 ± 13.4</td>
<td>50.9—116.6</td>
<td>66.7 ± 12.6</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2 ± 4.6</td>
<td>19.7—41.3</td>
<td>25.1 ± 4.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Total body BMD Z-score</td>
<td>−0.5 ± 0.8</td>
<td>−2.2—1.9</td>
<td>−0.4 ± 0.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Hip BMD Z-score</td>
<td>−0.0 ± 0.9</td>
<td>−1.4—2.0</td>
<td>0.1 ± 0.9</td>
<td>0.23</td>
</tr>
<tr>
<td>Lumbar spine BMD Z-score</td>
<td>0.2 ± 1.0</td>
<td>−1.5—2.9</td>
<td>0.1 ± 1.0</td>
<td>0.51</td>
</tr>
<tr>
<td>Mos since diagnosis</td>
<td>Median (Q1—Q3)</td>
<td>Min—Max</td>
<td>Median (Q1—Q3)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>15 (9—24)</td>
<td>1—124</td>
<td>12 (9—20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (94)</td>
<td>23 (92)</td>
<td>26 (100)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
</tbody>
</table>
Participants receiving NA+P exhibited stabilization of total body, lumbar spine, and hip BMD, BMD Z-scores, or BMC ($p_{\text{within}} > 0.30$ for all measures).

In NA+CEE group, both total body BMC and BMD increased over 12 mos ($BMD \ p=0.05$ and $BMC \ p<0.001$; $p_{\text{between}} = 0.02$)
No losses of total hip or lumbar spine BMD or BMC

Lean mass increased in NA+CEE by 12 mos (+1.4kg, $p=0.001$) but not in NA+P ($p_{\text{between}} = 0.006$)
No differences in fat mass seen ($p_{\text{between}} = 0.44$)
Results: QOL Measures

At baseline, overall scores for physical health (Physical Summary Score, PCS) in both add-back groups were significantly lower than the US mean (impaired). Baseline Mental Summary Scores (MCS) for both groups were not lower than the US mean.

Results: QOL Measures

While both groups improved over time ($p_{within} \leq 0.003$), the NA+CEE group showed greater increases in PCS score than the NA+P group ($p_{between} = 0.005$). Neither group showed significant changes in MCS over time ($p_{within} \geq 0.49$).

Results: Safety Measures
Conclusions

• Hormonal add-back successfully preserved bone health and improved QOL for adolescents with endometriosis treated with 12 mos of GnRHa
• Combination NA+CEE add-back appears to be more effective for increasing total body BMC, aBMD, lean mass, and physical health QOL than NA+P monotherapy
• No significant side effects of either regimen were observed

Limitations

• Sample was limited to skeletally mature young women
  – Results may not generalize to growing girls
• DXA measures provide 2-dimensional measures of BMD, and do not yield information regarding skeletal strength or microarchitecture
  – Future work will explore the effects of add-back on the peripheral skeleton and bone strength

Implications

• A combination regimen of oral NA+CEE appears to be safe and effective for increasing aBMD and BMC in young women with endometriosis during one year of GnRHa treatment, and superior to NA+P
• Given the prevalence of endometriosis, our data suggest NA+CEE to be a useful adjunctive therapy to prevent bone loss in young women while they receive appropriate medical treatment for their underlying disease
Acknowledgements

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