Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate (DMPA) contraceptive injections

Z Harel\(^1\); K Wolter\(^2\); MA Gold\(^3\); BA Cromer\(^4\); A Bruner\(^5\); M Stager\(^4\); L Bachrach\(^6\); R Brown\(^7\); P Hertweck\(^8\); A Nelson\(^9\); D. Nelson\(^10\); SM Coupey\(^11\); CC Johnson\(^12\); R Burkman\(^13\); H Bone\(^14\)

\(^1\)Hasbro Children's Hospital and Brown University, Providence, RI; \(^2\)Pfizer Inc New London, CT; \(^3\)University of Pittsburgh, Pittsburgh, PA; \(^4\)Metro-Health Medical Center, Cleveland, OH; \(^5\)Johns Hopkins University School of Medicine, Baltimore, MD; \(^6\)Stanford University School of Medicine, Stanford, CA; \(^7\)Temple University School of Medicine, Philadelphia, PA; \(^8\)University of Louisville School of Medicine, Louisville, KY; \(^9\)David Gefen School of Medicine at UCLA, Torrance, CA; \(^10\)Wayne state University School of Medicine, Detroit, Mich; \(^11\)Children’s Hospital at Montefiore, Bronx, NY; \(^12\)Henry Ford Health System, Detroit, MI; \(^13\)Baystate Medical Center, Springfield, MA; \(^14\)Michigan Bone and Mineral Clinic PC, Detroit, MI
DMPA
Progestin-only contraceptive method

Relative estrogen deficiency

Bone loss

Questions remain re:
1. Exact mechanisms of bone loss
2. Clinical implications of bone loss
Purpose:
To examine the impact of DMPA use on adolescents’ bone mineral density
Study Design

• **Design**
  - Open-label, nonrandomized, prospective, multicenter study

• **Subjects**
  - Females aged 12 to 18 years

• **Assessment during treatment and after D/C**
  - DMPA-IM every 12 wks for up to 240 wks
  - F/U after DMPA D/C for up to 240 wks
Study Design (cont)

- **BMD** of the lumbar spine and hip was measured at baseline and every 6 months by dual energy x-ray absorptiometry (DXA).

- **Bone formation markers** (serum osteocalcin and bone-specific alkaline phosphatase), **bone resorption marker** (urinary N-telopeptide), and **serum estradiol** were measured at baseline and every 6 months.

- Serum PTH and **25 (OH) vitamin D** levels were obtained from adolescents with > 5% BMD loss from baseline.
Study Design

• Participants
  - 181 adolescents provided data during DMPA use
  - 98 of these adolescents provided data after discontinuation (D/C) of DMPA
Unanswered Question #1

Why are some adolescent DMPA users loosing more bone than others?
To identify and characterize adolescents on DMPA-IM who experienced a BMD loss of $\geq 5\%$ from baseline in comparison with adolescents who lost $<5\%$
### Lumbar Spine BMD During DMPA use

<table>
<thead>
<tr>
<th></th>
<th>&lt; 5% BMD loss</th>
<th>≥ 5% BMD loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>136 (75)</td>
<td>45 (25)</td>
</tr>
<tr>
<td>No. of injections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>12 (p &lt;0.001)</td>
</tr>
<tr>
<td>Time to confirmed loss of ≥5% (wk)</td>
<td>N/A</td>
<td>123 83-209</td>
</tr>
<tr>
<td>Median Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 5% BMD loss (n=136)</td>
<td>≥ 5% BMD loss (n=45)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Age, yr, (SE)</td>
<td>15.5 (0.1)</td>
<td>15.7 (0.03)</td>
</tr>
<tr>
<td>Gyn age, months (SE)</td>
<td>46.5 (1.9)</td>
<td>48.5 (3.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Other (%)</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Mean BMI (SE)</td>
<td>23.7 (0.4)</td>
<td>23.1 (0.7)</td>
</tr>
<tr>
<td>Calcium serving/wk</td>
<td>24.4 (2.2)</td>
<td>20.7 (2.4)</td>
</tr>
<tr>
<td>Activity score</td>
<td>3.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>% Alcohol user</td>
<td>30</td>
<td>47 (p=0.043)</td>
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</tbody>
</table>
## Hip BMD During DMPA use

<table>
<thead>
<tr>
<th></th>
<th>&lt; 5% BMD loss</th>
<th>≥ 5% BMD loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>91 (50)</td>
<td>90 (50)</td>
</tr>
<tr>
<td>No. of injections</td>
<td>Median 7</td>
<td>12 (p &lt;0.001)</td>
</tr>
<tr>
<td>Time to confirmed loss of ≥5% (wk)</td>
<td>Median N/A</td>
<td>126 53-243</td>
</tr>
<tr>
<td></td>
<td>&lt; 5% BMD loss (n=91)</td>
<td>≥ 5% BMD loss (n=90)</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Age, yr, (SE)</td>
<td>15.5 (0.2)</td>
<td>15.6 (0.02)</td>
</tr>
<tr>
<td>Gyn age, months (SE)</td>
<td>49.3 (2.2)</td>
<td>44.7 (2.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Other (%)</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Mean BMI (SE)</td>
<td>24.6 (0.6)</td>
<td>22.4 (0.04)</td>
</tr>
<tr>
<td>Calcium serving/wk</td>
<td>27.3 (2.9)</td>
<td>20.6 (2.0)</td>
</tr>
<tr>
<td>Activity score</td>
<td>3.0</td>
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<td>33</td>
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<td>28</td>
<td>41</td>
</tr>
</tbody>
</table>
Estradiol levels in adolescents during use of DMPA – Mean (SE)

* p<0.05
Estradiol Levels in Adolescents by Lumbar Spine BMD Change - Mean (SE)

Week 120

- (n=49) < 5% BMD loss
- (n=21) ≥ 5% BMD loss

Week 180

- (n=36) < 5% BMD loss
- (n=15) ≥ 5% BMD loss

*NS
Estradiol Levels in Adolescents by Hip BMD Change – Mean (SE)

Week 120

- (n=27)
- (n=43)

< 5% BMD loss

> 5% BMD loss

Week 180

- (n=16)
- (n=35)

*NS
25 (OH) D and PTH levels in adolescents with substantial (≥ 5%) BMD loss

25 (OH) D mean (SD) levels (ng/mL)  
- Deficient  
- Insufficient  
- Normal range = 7-53 pg/mL

PTH mean (SD) levels (pg/mL)  
- (n=14)

(n=15)
Conclusions

Substantial BMD decreases of $\geq$ 5% were observed in
- 25% of adolescents at the lumbar spine
- 50% of adolescents at the hip

DMPA-IM induced a relative estrogen deficiency, but the decrease did not correlate with the magnitude of BMD loss

Lower BMI, insufficient calcium and vitamin D intake, and alcohol use, were associated with a greater BMD loss
Unanswered Question #2

What is the pattern of BMD recovery after discontinuation of DMPA?

Harel et al. Contraception 2010
Recovery of lumbar spine (LS) bone mineral density after DMPA D/C

- Mean LS BMD recovered to pre-treatment levels 60 weeks after the last DMPA injection, and then continued to increase at all subsequent time points to 240 weeks.
- By 240 weeks after DMPA discontinuation, 84% of participants had a LS BMD value that exceeded their baseline value, and the mean LS BMD value was 4.7% greater than at baseline.
Recovery of hip bone mineral density after DMPA Discontinuation (D/C)

- BMD changes following DMPA D/C occurred more slowly at the hip.
- Full recovery of mean BMD to baseline value at the total hip (TH) required 240 weeks and at the femoral neck (FN) at least 180 weeks.

- By 240 weeks after DMPA D/C:
  - 56% of participants had a TH BMD value that exceeded their baseline value,
  - 40% had a FN BMD value that exceeded their baseline value.
BMD loss in female adolescents receiving DMPA for contraception is substantially or fully reversible in most girls following discontinuation of DMPA, with faster recovery at the LS than at the hip.
Does calcium intake affect the extent of BMD recovery after DMPA discontinuation?

Harel et al. Contraception 2010
Mean % change from baseline in **Lumbar Spine BMD** after DMPA D/C, by calcium intake

Harel et al. Contraception 2010
Mean % change from baseline in Femoral Neck BMD after DMPA D/C, by calcium intake

Harel et al. Contraception 2010
Unanswered Question #4

Does the extent of BMD loss during use of DMPA affect the extent of BMD recovery after discontinuation?

Harel et al.
Contraception 2010
Mean % Change from Baseline in **Lumbar Spine BMD** after DMPA D/C in participants with and without BMD losses of ≥5% during DMPA use

Harel et al. Contraception 2010
Mean % Change from Baseline in Total Hip BMD after DMPA D/C in participants with and without BMD losses of \( \geq 5\% \) during DMPA use

Harel et al. Contraception 2010
The final question

Do we need to minimize the BMD loss during use of DMPA in adolescents?
Ways of minimizing the decrease in bone mineral density

(+) Adequate calcium intake (1300 mg/day)
(+) Adequate vitamin D intake (400 IU or more)
   Assess serum total 25OH vitamin D level
(+) Regular weight bearing physical activity
(+) Avoid smoking and alcohol
(?) Periodic add-back of estrogen
(?) Phytoestrogens
Thank you for your kind attention!