Retrospective Cohort Study of DMPA and Fractures in Reproductive Age Women

Andrew Kaunitz*, Ze’ev Harel**, Henry Bone***, Quazi Ataher^, Doug Ross^, Philip Arena^, Kevin Wolter^
Author Disclosures

- **Kaunitz:**
  - no disclosures re Pfizer
  - clinical trial support and consulting with Teva

- **Harel:**
  - clinical trial support with Pfizer

- **Bone:**
  - clinical trial and consulting support with Pfizer

- **Ataher, Ross, Arena, Wolter:**
  - employees of Pfizer
DMPA Chronology

- **1960s**: Widely used in family planning programs in Thailand, Indonesia, Mexico
- **1992**: FDA approved DMPA for contraception and mandated post-approval BMD studies
- **1992-2003**: Use for contraception in the US increased:
  - ~2 million users as of 2002
  - One quarter of US women ages 15-25 have used DMPA
  - Declines in rates of teen pregnancy and abortion
- **2005**: FDA approved DMPA 104 mg subQ

DEPO-PROVERA®
Contraceptive Injection
medroxyprogesterone acetate injectable suspension, USP

Pharmacia

Physician Information

Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.

It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate. (See WARNINGS.)
Impact of Black Box: Florida OB/GYN Physicians

- Almost half of respondents now restrict duration of DMPA use
- Two thirds order bone density assessments in DMPA users
- Some respondents indicated they prescribe bisphosphonates to women using DMPA

DMPA lowers serum E2 and BMD

Mean BMD decline is 4% to 7% (spine, hip)

- BMD decline observed in adults & adolescents
- BMD decline is reversible after treatment is discontinued – E2 increases post-treatment
- Bone loss with DMPA is analogous to transient BMD decline during pregnancy and lactation

- A Kaunitz et al. Contraception, 2006
- Z Harel et al. Contraception, 2010
Correlation between BMD and fracture risk is well established – but only in post-menopausal women.

HYPOTHESIS: The transient BMD decline caused by DMPA (~ 5% decline) would need to cause a deterioration of bone micro-architecture that is sufficient to increase the incidence of FRAGILITY (atraumatic, osteoporotic) fractures.

COROLLARY: DMPA-induced BMD change would not be expected to increase incidence rate of TRAUMATIC fractures, which are substantially unrelated to BMD changes.
Two recent Case Control studies showed that DMPA users have more fractures than non-users.
**2008 National Danish Case-control Study of DMPA and Fracture**

- **DMPA use rare:** only 0.1% of study population used DMPA (N=163)
  - OR for DMPA use = **1.44** (95% CI 1.01-2.06); ORs higher with longer-term DMPA use
  - In contrast, OR for IUD use = 0.75 (95% CI 0.64-0.87)

- **Cases w/fracture (N=64,548) compared to controls w/o fracture (193,641);** DMPA (and IUD) use was assessed

- **Authors pointed out** ‘…use of injectable contraception is so rare in Danish women that it is likely that baseline characteristics among DMPA users… do not reflect the characteristics of contraceptive users overall.’
  - Alcoholism: 14% in DMPA users, 2% in IUD users (p<.01)

2010 UK Case-control Study of DMPA and Fracture

- Investigators used General Practice Research Database (GPRD)
- Cases w/fx (N=17,527) compared to controls (70,130)
- DMPA ever-use ~10%
- Adjusted ORs for DMPA use: 1.17 to 1.54
  - ORs higher with longer-term DMPA use

- C Meier, et al. J Clin Endocrinol Metab 2010
Advantage of a COHORT study: Allows separation of timing of DMPA use and time of fracture
UK Retrospective Cohort Study using the GPRD: Study Design

Objective:

- Compare fracture rates between DMPA users & users of other hormonal contraceptives (predominantly OC)

Entry Criterion: 1st hormonal contraceptive prescription < Age 50

“Index Date” = date of the woman’s first DMPA injection (or 1st OC prescription)

Endpoint = incident fracture
Result: DMPA users had more fractures…

- In the Full Cohort (all women; N = 312,385), fractures were assessed after the Index Date:
  - Median f/u 5.5 years following first prescription
  - 42,204 women followed for 10 to <15 years
  - 14,253 followed for 15 or more years
- 2935 fxs / 79,065 DMPA users (327,315 PY)
- 8887 fxs / 233,330 Non-users (1,395,040 PY)
- Incident Rate Ratio = 1.41 (95% CI: 1.35, 1.47)^

^ Age was the only confounding variable; age-adjusted RR = 1.44 (95%CI: 1.38, 1.50). Adjustment for each of the other potential confounders, for which data were available, did not result in a meaningful difference when age was already adjusted for; PY = person years.
Fracture Risk vs. Time Since First DMPA Injection

Observed fracture risk was higher *BEFORE* any BMD loss could have occurred

Rate in non-users is constant by definition: no DMPA injection
Fracture rate before first DMPA injection

A **Subcohort** (53% of the full cohort) had data available for the 6-month period preceding the Index Date (i.e., pre-treatment data).

<table>
<thead>
<tr>
<th>Fractures occurring in the SUBCOHORT</th>
<th>N</th>
<th># fractures</th>
<th>Person-years (PY) of exposure time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPA users</td>
<td>41,876</td>
<td>176</td>
<td>20,938</td>
</tr>
<tr>
<td>Non-users</td>
<td>124,491</td>
<td>409</td>
<td>62,246</td>
</tr>
<tr>
<td><strong>After the INDEX DATE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPA users</td>
<td>41,876</td>
<td>1574</td>
<td>173,713</td>
</tr>
<tr>
<td>Non-users</td>
<td>124,491</td>
<td>4939</td>
<td>44,242</td>
</tr>
</tbody>
</table>
## Summary of Relative Fracture Risk (any fracture)

<table>
<thead>
<tr>
<th></th>
<th>Fx/1000 PY</th>
<th></th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMPA</td>
<td>Non-users</td>
<td></td>
</tr>
<tr>
<td><strong>DMPA vs Non-User: AFTER INITIATION of TRT (full cohort)</strong> ^</td>
<td>9.0</td>
<td>6.4</td>
<td>1.41 (1.35-1.47)</td>
</tr>
<tr>
<td><strong>DMPA vs Non-User: PRIOR to TRT (sub-cohort)</strong></td>
<td>8.4</td>
<td>6.6</td>
<td>1.28 (1.07-1.53)</td>
</tr>
<tr>
<td><strong>DMPA vs Non-User: AFTER INITIATION of TRT (sub-cohort)</strong></td>
<td>9.1</td>
<td>6.6</td>
<td>1.37 (1.29-1.45)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>PRE-TRT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DMPA Users: Post- vs Pre-initiation of DMPA (subcohort)</strong></td>
<td>8.4</td>
<td>9.1</td>
<td>1.08 (0.92-1.26)</td>
</tr>
<tr>
<td><strong>Non-Users: Post- vs Pre-initiation of non-DMPA Contraceptive (subcohort)</strong></td>
<td>6.6</td>
<td>6.6</td>
<td>1.01 (0.91-1.12)</td>
</tr>
</tbody>
</table>
Analysis by Fracture Type Was Performed

- **What types of fracture occurred more often in DMPA users?**
  - All fractures?
  - Or only those known to be sensitive to BMD changes?

- **Is there a ‘dose-response’?**
  - Is risk related to duration of DMPA exposure?

These key questions address if the observed findings might be biologically related to DMPA use.
# Fracture Risk by Anatomic Site (Full Cohort; Post-Index Date)

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Fx / 1000 PY</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMPA</td>
<td>Non-user</td>
</tr>
<tr>
<td>Axial (vertebrae, hip, pelvis)</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>Appendicular Skeleton (arm, leg, wrist, ankle, hand, foot, clavicle, rib/sternum, and shoulder)</td>
<td>4.96</td>
<td>3.59</td>
</tr>
<tr>
<td>All Other Fractures (e.g., finger, toe, skull, face, multiple trauma &amp; unspecified)</td>
<td>3.78</td>
<td>2.54</td>
</tr>
</tbody>
</table>
### Fracture rate by number of injections: No Dose-Response Observed

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Fractures</th>
<th>Fractures per 1,000 Pt-Years</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Users</td>
<td>8,887</td>
<td>6.4</td>
<td>reference</td>
</tr>
<tr>
<td>Number of DMPA Injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 7 Injections</td>
<td>2288</td>
<td>9.4</td>
<td>1.47 (1.40-1.54)</td>
</tr>
<tr>
<td>≥ 8 Injections</td>
<td>647</td>
<td>7.8</td>
<td>1.22 (1.13-1.32)</td>
</tr>
</tbody>
</table>
Summary

The observed higher fracture rate in DMPA users does not appear to be due to DMPA use

- Higher fx rate was present before DMPA initiated
- Fx rate did not increase after DMPA was started
- Fx rate did not increase with a greater number of DMPA injections

The higher fracture rate in DMPA users does not appear to be linked to low BMD

- ‘Fragility’ fracture rate was not higher in DMPA users
- Trauma-related fractures did occur at a higher rate
Retrospective Cohort Study of DMPA Use and Fractures: Conclusions I.

- DMPA represents an important contraceptive option for women in the US and abroad.

- The FDA Black Box and recent publications suggesting DMPA use “increases fracture risk” in young women have generated unwarranted concerns about DMPA safety.
Our study does not address the potential for a latent effect - decades after DMPA was used

- E.g., young adult usage → fractures in the elderly

However, among menopausal women, it has been shown that prior DMPA use is not associated with lower BMD (vs non-users)*

Retrospective Cohort Study of DMPA Use and Fractures

- Thank you!

- Questions?