WEIGHT GAIN AND UNSCHEDULED BLEEDING ON THREE DOES OF DEPOT MEDROXYPROGESTERONE ACETATE: A RANDOMIZED TRIAL IN ADOLESCENTS

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Background

• Weight gain & unscheduled bleeding are highly variable among adolescents on DMPA.
• Despite a wide variety of studies examining predictors of DMPA-associated side effects, understanding of who is at risk is limited.
DMPA Pharmacokinetics

• Wide inter-individual variability
• Contraceptive threshold = 0.1 ng/ml
• 12-week serum concentration ranges from <0.04 ng/ml - 2.6 ng/ml

DMPA Pharmacokinetics

• Single IM doses of 25, 50, and 100 mg have been shown to inhibit ovulation for at least 3 months in most individuals.
• The relationship between DMPA exposure and side effects is not known.

Study Objective

The objective of this study was to assess associations between MPA exposure with weight gain and unscheduled bleeding in adolescents initiating DMPA.
Study Methods

- Subjects - healthy post-menarcheal females, 12-21 years, initiating DMPA
- Exclusion Criteria
  - chronic disease or medication known to affect weight
  - DMPA use within the past 12 months
  - pregnancy within the past 6 months
  - implant, IUD or combined hormonal contraceptive use within the past 3 months
  - weight exceeding DXA scanner limit (350 lbs)
  - need for confidential contraceptive care for those < 18 years

Study Methods

- IRB approval obtained for study protocol.
- Consent
  - Written informed consent from subjects ≥18 and 1 legal guardian of subjects <18
  - Written informed assent from subjects <18
- Randomized to 1 of 3 DMPA doses
  - 150, 104, or 75mg
  - All given IM every 12 weeks

Data Collection

- Weight/Adiposity at 0, 12, and 24 weeks.
- Standardized diary card to record total # days of unscheduled bleeding/spotting.
- Serum MPA, estradiol, and progesterone
  - Weekly from 0 – 12 weeks
  - At 16, 20, and 24 weeks
- MPA/progesterone measured by highly sensitive LC-MS/MS method.
**Safety Protocol**

Dose escalation in any subject who met either alarm value:
- MPA concentration < 0.3 ng/ml
  
  OR
  
  - Progesterone concentration ≥ 2 ng/ml

**Data Analyses**

- **Intent to Treat Analysis**
  - Main outcome measures
    - Weight & adiposity at 24 weeks
    - total # days bleeding/spotting
  - PK measures
    - \( C_{\text{max}} \)
    - \( T_{\text{max}} \)
    - \( K \) (elimination constant)
    - \( \text{AUC}_{0-12 \text{ weeks}} \)

**Study Consort Diagram**
Subject Demographics

- Race
  - 65% White, 35% Black
- Age
  - Mean chronological age 18.5 (12.4 – 21.6)
  - Mean gynecologic age 6.1 (0.4 – 9.7)
- Dose escalation
  - 3 of 10 (30%) 75mg subjects
  - MPA >0.01ng/ml in 98% of dose intervals

Weight Gain at 24 weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>150mg</th>
<th>104mg</th>
<th>75mg</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in BMI (kg/m²)</td>
<td>Mean (SD)</td>
<td>0.2 (1.40)</td>
<td>0.9 (1.12)</td>
<td>0.3 (1.34)</td>
</tr>
<tr>
<td>% Change in Body Fat</td>
<td>Mean (SD)</td>
<td>1.6 (3.51)</td>
<td>3.2 (2.72)</td>
<td>2.1 (2.99)</td>
</tr>
<tr>
<td>&gt;5% Weight Gain (n,%)</td>
<td>1 (12.5)</td>
<td>2 (22.2)</td>
<td>2 (28.6)</td>
<td>5 (20.8)</td>
</tr>
</tbody>
</table>

Bleeding/Spotting 0-24 weeks

![Bleeding/Spotting Graph]

Days of Bleeding/Spotting by Dose Cohort

- Days Bleeding
- Days Spotting
- Combined Days Bleeding/Spotting
Spearman’s Rho Correlation Matrix: PK parameters and outcomes

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Δ BMI</th>
<th>Δ % Body Fat</th>
<th># Days Bleeding</th>
<th># Days Spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max</td>
<td>-0.248</td>
<td>-0.199</td>
<td>0.203</td>
<td>0.015</td>
</tr>
<tr>
<td>T_max</td>
<td>0.083</td>
<td>-0.053</td>
<td>-0.525**</td>
<td>-0.144</td>
</tr>
<tr>
<td>K (elimination constant)</td>
<td>-0.045</td>
<td>0.036</td>
<td>0.319</td>
<td>-0.362</td>
</tr>
<tr>
<td>AUC 0-12 weeks</td>
<td>-0.327*</td>
<td>-0.357*</td>
<td>0.162</td>
<td>0.200</td>
</tr>
</tbody>
</table>

** p < 0.01  	* p < 0.10

Multivariate Regression: Bleeding/spotting outcome

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>82.93</td>
<td>9.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T_max</td>
<td>-0.98</td>
<td>9.94</td>
<td>0.005</td>
</tr>
<tr>
<td>75mg Dose</td>
<td>-0.43</td>
<td>0.31</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Backwards elimination stepwise regression eliminating insignificant (p>0.10) independent variables. Potential predictors included race, baseline BMI, DMPA dose, PK parameters.
Conclusions

• 75mg DMPA provided effective contraception in 70% of subjects.
• A trend for an inverse relationship between MPA exposure (AUC) and weight gain was observed.
• MPA PK parameters ($T_{max}$) better predicted unscheduled bleeding than did DMPA dose.

Implications/Future Directions

• Adolescents can be enrolled in rigorous contraceptive trials.
• Lower dose DMPA may provide equal efficacy with similar tolerability.
• 48-week BMD data in this study cohort is pending.
• An easily obtainable PK marker would ↑ clinical utility of findings.