A Phase II, Dose-Finding, Crossover Study to Evaluate the Effect of a Transdermal Nestorone®/Estradiol (NES/E2) Gel On Ovulation Suppression and Assess Acceptability in Healthy Ovulating Women

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Population Council Mission

Improve the well-being and reproductive health of current and future generations around the world and help achieve a humane, equitable and sustainable balance between people and resources.
Reproductive Health and Social Context
Striving to Achieve MDG 4 & 5

• Increased demand for contraceptive services by 40% (535 to 746 million users) by 2025

• Half a million women die in pregnancy and childbirth every year

• More than 5% (105 million) of women report unmet need for contraception
  
  – *Need for innovative methods that are safe, effective, acceptable*
NESTORONE®

- Derived from Progesterone
- Highest antiovulatory activity
- High progestational potency
- Not active orally, not bound to SHBG
- No androgenic or estrogenic effect
- Potent antiestrogenic action >LNG
- No glucocorticoid effect at contraceptive doses
- An ideal progestin for transdermal use
Potential Benefits of Progestins with no androgenic activity

- no weight gain
- no acne
- no adverse effect on lipids
- minimal impact on glucose and insulin
- Should have less impact on the vessels and vasomotion
NES/E2 Gel Development Concept

- NES to ensure ovulation inhibition
- Target serum levels proven to correlate with high % of anovulation
- Use estradiol (and not ethinyl estradiol) add-back therapy to prevent hypoestrogenism
- Aim to target a safer contraception with “natural” steroids
  - Potential for lower risk of thrombosis
• A Phase II, dose finding, cross-over study to evaluate the effect of NES/E2 transdermal gel delivery on ovulation suppression in 18 normal ovulating women

• Primary Objective: To determine the lowest effective dose of 3 formulations of NES/E2 gel to suppress ovulation in 90-95% of cycles
NES/E2 Gels: Percentage of ovulatory cycles (Follicle rupture & P↑) among compliant women based on detectable NES

- Low Dose: NES (mg/d) = 1.5, E2 (mg/d) = 0.5, n=15
- Medium Dose: NES (mg/d) = 3.0, E2 (mg/d) = 1.0, n=15
- High Dose: NES (mg/d) = 4.5, E2 (mg/d) = 1.5, n=16

Total suppression of ovulation in compliant subjects

*Unpublished results*
NES/E2 gel
Bleeding Pattern

• Minimal breakthrough bleeding during 3 weeks of use
• No major differences between doses, although there was a tendency for more breakthrough bleeding using the lowest dose
NES/E2 gel

Conclusions

- Ovulation suppression was achieved with all doses
- No apparent correlation of NES serum levels with BMI and body weight
- Follicular development ≥ 16 mm observed in 40%, 13% and 6% of the low, medium and high dose cycles
NES/E2 gel
Conclusions

- Medium dose (NES 3.0 / E2 1.0 mg/d) seems to provide adequate:
  - Ovulation inhibition
  - Inhibition of follicular development ≥ 16 mm
  - Estradiol replacement levels (mid-follicular E2 levels)
  - Bleeding control for 21 days
CONCLUSIONS

• Nestorone® exerts high antiovulatory effect at low doses

• Non androgenic progestins should induce fewer side-effects

• Transdermal estradiol (E2) shown to induce less thrombosis than oral E2 in hormone therapy
  – Combining natural estradiol (E2) instead of ethinyl estradiol (EE) should decrease EE-related risks

• NES/E2 gel will be the first transdermal contraceptive with E2
Acceptability Study
What do Women Think of this Method?

• Open-ended questionnaire administered at end of study to all participants
• Questions addressed:
  – Subjective parameters, e.g. satisfaction
  – Objective parameters
    • Ease of use, general likes/dislikes
    • Partner responses,
    • Side effects
    • Willingness to purchase product
Positive Aspects of NES/E2 Gel
Three Themes

• *Gel is easy to use*
  – Easier to administer than OCs
  – Less invasive than injectables/IUDs
  – Easy to remember schedule (part of evening hygiene routine)
  – Absorbs quickly

• *Fewer side effects than other methods*
  – Didn’t irritate skin
  – Unnoticeable after absorbed
Positive Aspects of NES/E2 Gel

Three Themes

• Positive physical effects
  – Felt cool on skin (pleasant and refreshing)
  – Perceived positive effects on skin & hair
    • Smoother, shinier
Negative Aspects of NES/E2 Gel System

• 13/16 women had no negative comments about gel
  – 3 women reported negative aspects of gel
    • Increased bleeding- 1
    • Absorption of gel took time- 2

• 13/16 women had no negative reports about delivery system
  – 3 women reported application problems
    • Template for applying gel cumbersome-1
    • Dispenser/Pump complaints -2

1 participant reported both a gel & delivery system complaint
Conclusions to the Acceptability Study

• A small sample of women from 3 global regions found NES/E2 gel acceptable
  – Easy to use, easy to remember
  – Desirable in terms of lack of side effects
    • Issue of bleeding needs further study/evaluation
  – No negative effect on partners
• Women willing to pay, recommend to others
• Potential skin/hair benefit reports of interest

Further study in larger, more diverse populations needed to demonstrate safety, efficacy & acceptability
Acknowledgements

• Population Council

• Antares

• Women and collaborators at 3 Study Sites

THANK YOU!
Classification of Progestins

Derived from Progesterone

- 17-OH Progesterone
  - Medroxyprogesterone Ac
  - Cyproterone Ac
  - Chlormadinone Ac
  - Megestrol Ac
- 19-nor progesterone
  - Nestorone
  - Nomegestrol ac
  - Trimegestone (←R5020)
- Spirolactone
  - Drospirenone

Derived from Testosterone

- Estranes
  - Norethisterone
  - Dienogest
- Gonanes
  - Levonorgestrel
  - Desogestrel (etonogestrel)
  - Gestodene
  - Norgestimate (norelgestromin)
Study Design

• 18 healthy, ovulating women at 3 sites (Chile, Dominican Republic & USA/ LA)
• Crossover design to evaluate three doses of NES/E2 Gel, each participant receiving each dose
  – High (4.5mg NES/1.5mg E₂)
  – Medium (3.0mg NES/1.0mg E₂)
  – Low (1.5mg NES/0.5mg E₂)
• Qualitative Acceptability Study
# NES/E2 gel

## Age, weight and BMI of participants

<table>
<thead>
<tr>
<th></th>
<th>DR Site Mean ± S.D. N = 6</th>
<th>Chile Site Mean ± S.D. N = 6</th>
<th>LA (USA) Site Mean ± S.D. N = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>33.0 ± 4.8</td>
<td>35.8 ± 2.4</td>
<td>32.0 ± 5.5</td>
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<tr>
<td><strong>Weight (kg)</strong></td>
<td>59.9 ± 9.7</td>
<td>64.9 ± 6.2</td>
<td>70.0 ± 5.3</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>24.6 ± 3.9</td>
<td>25.2 ± 1.6</td>
<td>27.4 ± 0.7</td>
</tr>
</tbody>
</table>

* Unpublished results
NES/E2 Gel (All subjects included)
Percentage of ovulatory cycles (Follicle rupture & P↑)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>NES (mg/d)</th>
<th>E2 (mg/d)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>1.5</td>
<td>0.5</td>
<td>17</td>
</tr>
<tr>
<td>Medium Dose</td>
<td>3.0</td>
<td>1.0</td>
<td>16</td>
</tr>
<tr>
<td>High Dose</td>
<td>4.5</td>
<td>1.5</td>
<td>17</td>
</tr>
</tbody>
</table>

* Unpublished results
Prot 427: NES/E2 gels
NES levels during 21 days of treatment

Dose-response of NES serum levels; target levels 250 pmol reached

*Unpublished results
E2 levels were consistent with mid-follicular phase levels (~120pg/ml)
NES/E2 Gels: Maximum follicular development (mm) during 21 d continuous gel use

High % of large follicles with the lower dose

<table>
<thead>
<tr>
<th>Follicle Category</th>
<th>Low dose (n = 15)</th>
<th>Medium dose (n = 15)</th>
<th>High dose (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>27</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>11-15</td>
<td>33</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>≥ 16</td>
<td>40</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

NES (mg/d) : 1.5  3.0  4.5
E2 (mg/d): 0.5  1.0  1.5

*Unpublished results
### Number of bleeding and spotting days during 21 days of gel use

<table>
<thead>
<tr>
<th></th>
<th>Low dose</th>
<th>Medium dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding days</strong></td>
<td>0.7 ± 1.2</td>
<td>0.4 ± 1.3</td>
<td>0.5 ± 1.1</td>
</tr>
<tr>
<td><strong>Spotting days</strong></td>
<td>1.9 ± 3.2</td>
<td>1.0 ± 2.3</td>
<td>1.1 ± 1.9</td>
</tr>
<tr>
<td><strong>Bleeding+ Spotting</strong></td>
<td>2.6 ± 3.7</td>
<td>1.4 ± 2.5</td>
<td>1.6 ± 2.6</td>
</tr>
</tbody>
</table>

Bleeding that occurred during first 3 days of gel use is not included.

Gel use began day 1-4 of the cycle.

* Unpublished results

Fewer spotting days with the medium and high doses