Evidence of Low Androgenicity and Little Impact on Sexual Function or Activity with Annovera™, a Novel Contraceptive Vaginal System Releasing Segesterone Acetate and Ethinyel Estradiol

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Disclosures

• **Advisory board member**: AMAG

• **Consultant**: Dare, JDS Therapeutics, Sprout, Strategic Scientific Technologies (SST), TherapeuticsMD, and Proctor & Gamble

• **Writing support**: AMAG and TherapeuticsMD
Background

- Combined hormonal contraceptives (CHCs) may impact sexual function, in part due to interaction of the progestin component with the androgen receptor
- Some CHCs have been previously reported to decrease or increase libido
- Annovera™ is a new contraceptive vaginal system (CVS) recently approved by the FDA (August 2018)
  - Ring-shaped CVS
  - Releases 150 mcg segesterone acetate (SA) and 13 mcg ethinyl estradiol (EE) per day
  - 21-day in, 7-day out pattern for up to 1 year (13 cycles)
  - PEARL index: 2.98 (women ≤35 years of age)

Pearl Index = (# of pregnancies * 1300)/(# of on-therapy cycles)
Objective

• To review evidence from preclinical studies investigating the androgenicity of the SA component of the CVS
• To report the impact of the CVS on sexual function or activity in women who used the CVS for 1 year during a multi-country phase 3 trial
Progestational Effects of Progestins

SA has high progestational potency

SA has highest antiovulatory activity

McPhail Index

SA 100 > LNG 10 > Progesterone 1

SA 30 > LNG 10 > Progesterone 1

SA has high progestational potency

SA has highest antiovulatory activity

McPhail Index: endometrial transformation test.

SA Preclinical Data Summary

• No androgenic or estrogenic effect,\textsuperscript{1,2} does have antiestrogenic activity\textsuperscript{1}
  
  • Androgenic progestins such as LNG have agonist activity at the androgen receptor and stimulate androgenic target tissues\textsuperscript{1,2}

• Not orally active, not bound to SHBG\textsuperscript{1}

• No glucocorticoid effect at contraceptive doses\textsuperscript{1}

13SA: 13 ethyl SA; AR: androgen receptor; LNG: levonorgestrel; SA: segesterone acetate; SHBG: steroid hormone binding globulin.

Does the SA/EE CVS Impact Sexual Function?

- Phase 3 clinical trial at 12 sites in US, Latin America, Europe, and Australia (2006-2009)
- CVS was used for 13 cycles: 21 days in and 7 days out during each cycle
- Participants completed a questionnaire, that included sexual domain questions
  - At baseline and study end
  - 80% (905/1135) of women completed the questionnaire
  - Mean age 27 years; most were white (80%) and had at least some college education (63%)

**Inclusion Criteria**

- Healthy, sexually active women
- 18 to 40 years old
- Body mass index <29 kg/m²
- No medical contraindications to CHC use
- Not sterilized
- No use of monthly injectable contraceptives ≤2 months of study initiation or DMPA use ≤6 months
### Sexual Health Questions

<table>
<thead>
<tr>
<th>Questions</th>
<th>Choices</th>
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<tbody>
<tr>
<td>1. Feel ring during sex?</td>
<td>Never or ever</td>
</tr>
<tr>
<td>2. Partner feels ring during sex?</td>
<td>Never, ever, or don’t know</td>
</tr>
<tr>
<td>3. Change in frequency of sex?</td>
<td>No change or increased, decreased</td>
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<td>4. Change in sexual pleasure?</td>
<td>No change or increased, decreased</td>
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<tr>
<td>5. Ring affects partner sexual pleasure?</td>
<td>Never, ever, or don’t know</td>
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</tbody>
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- Results were stratified as “CVS removers” (n=120, removed CVS for >2 hours per cycle outside of scheduled removal periods) versus “nonremovers” (n=785)
- Women who removed the CVS >2 unscheduled hours in a cycle were 4 times more likely to get pregnant than nonremovers
  - OR 4.07 (95% CI 1.58-10.50)

Feel the Ring (CVS) During Sex?

- 31% of women could feel the ring during sex
  - Feeling the ring was associated with CVS removal >2 h ($P=0.012$)
- About half of partners could feel the CVS during sex

![Bar chart for women and partners](chart.png)

### Change in Frequency of Sex

- Frequency of sex increased or did not change in the majority of CVS users

<table>
<thead>
<tr>
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<th>Total (n=905)</th>
<th>Nonremovers (n=785)</th>
<th>CVS Removers (n=120)</th>
</tr>
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<tbody>
<tr>
<td>Women (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change or increased</td>
<td>84</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>Decreased</td>
<td>16</td>
<td>17</td>
<td>14</td>
</tr>
</tbody>
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Change in Sexual Pleasure

- In most CVS users, sexual pleasure increased or did not change

![Bar chart showing change in sexual pleasure]

- Total (n=905): 86 women (No change or increased), 14 women (Decreased)
- Nonremovers (n=785): 86 women (No change or increased), 14 women (Decreased)
- CVS Removers (n=120): 89 women (No change or increased), 11 women (Decreased)
Ring (CVS) Effects on Partner’s Sexual Pleasure

- In most users, the CVS did not affect their partner’s sexual pleasure
  - Effects of the ring on a partner’s sexual pleasure was associated with ring removal >2 h ($P=0.002$)

![Bar chart showing the percentage of Never, Ever, and Don't know responses for Total, Nonremovers, and CVS Removers.](chart.png)

Conclusions

• Binding affinity and animal studies show that the SA component of Annovera was not associated with androgenic effects that are potentially detrimental to sexual function\(^1\)-\(^3\)
  • SA is a strong progesterone receptor agonist with no androgenic properties

• In a phase 3 trial, the CVS did not have a negative impact on sexual function and activity\(^4\)
  • Majority of women (>80%) reported increased or unchanged
    • Frequency of sex
    • Sexual pleasure